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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	206538
Supporting document/s:	NDA 021081 (Lantus)
Applicant's letter date:	April 24th 2014
CDER stamp date:	April 25th 2014
Product:	Toujeo SoloStar
	Insulin Glargine [rDNA origin] 300 U/mL
Indication:	Adults (T1DM) and (T2DM)
Applicant:	Sanofi
Review Division:	DMEP
Reviewer:	Jeffrey Quinn
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1 Executive Summary

1.1 Introduction

Insulin glargine is a recombinant human insulin analog that represents a long-acting, parenteral blood glucose-lowering agent. Insulin glargine has been registered and marketed in the U.S. since April 20, 2000 as Lantus (insulin glargine [rDNA origin] injection, 100 U/mL) for once daily subcutaneous (SC) administration to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus (T1DM) and in adults with type 2 diabetes mellitus (T2DM).

Sanofi is seeking approval for the proposed indication: Improve glycemic control in adults with diabetes mellitus in response to subcutaneous administration of a new formulation of insulin glargine (HOE901-U300) that has the same composition as the current commercial formulation (Lantus), with adjustment of 3-times the amount of active pharmaceutical ingredient and corresponding zinc content, under this NDA. The proprietary name Toujeo SoloStar was granted for HOE901-U300 by the Agency on July 7th 2014.

1.2 Brief Discussion of Nonclinical Findings

- The toxicological data submitted for the approval of Lantus (insulin glargine, 100 U/mL) supports NDA 206538 given the minor formulation changes represented in the Toujeo SoloStar (insulin glargine, 300 U/mL) drug product.

- A local tolerance study was conducted with Toujeo SoloStar (300 U/mL) as a bridge to the Lantus (100 U/mL) drug product. Both formulations of insulin glargine displayed favorable local tolerance profiles in rabbits following subcutaneous injection which is the intended clinical route of administration.

1.3 Recommendations

1.3.1 Approvability

Pharmacology/Toxicology supports approval of NDA 206538

1.3.2 Additional Non Clinical Recommendations

No additional nonclinical studies are required.

1.3.3 Labeling

Established Pharmaceutical Class

Insulin glargine (HOE901) is classified in the pharmacotherapeutic group “Antidiabetic agent” (Anatomic Therapeutic Chemical [ATC] classification code: A10AE04 Insulin and analogues, long-acting).

1. INDICATIONS AND USAGE

Toujeo SoloStar is indicated to improve glycemic control in adults with diabetes mellitus.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4)

Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. Insulin glargine was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 50 times the recommended human subcutaneous starting dose of 0.2 Units/kg/day (0.007 mg/kg/day). In rabbits, doses of 0.072 mg/kg/day, which is approximately 10 times the recommended human subcutaneous starting dose of 0.2 Units/kg/day (0.007 mg/kg/day), were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In mice and rats, standard two-year carcinogenicity studies with insulin glargine were performed at doses up to 0.455 mg/kg, which was for the rat approximately 65 times the recommended human subcutaneous starting dose of 0.2 Units/kg/day (0.007 mg/kg/day). The findings in female mice were not conclusive due to excessive mortality in all dose groups during the study. Histiocytomas were found at injection sites in male rats (statistically significant) and male mice (not statistically significant) in acid vehicle containing groups. These tumors were not found in female animals, in saline control, or insulin comparator groups using a different vehicle. The relevance of these findings to humans is unknown.

Insulin glargine was not mutagenic in tests for detection of gene mutations in bacteria and mammalian cells (Ames- and HGPRT-test) and in tests for detection of chromosomal aberrations (cytogenetics *in vitro* in V79 cells and *in vivo* in Chinese hamsters).

In a combined fertility and prenatal and postnatal study in male and female rats at subcutaneous doses up to 0.36 mg/kg/day, which was approximately 50 times the recommended human subcutaneous starting dose of 0.2 Units/kg/day (0.007 mg/kg/day), maternal toxicity due to dose-dependent hypoglycemia, including some deaths, was observed. Consequently, a reduction of the rearing rate occurred in the high-dose group only. Similar effects were observed with neutral protamine Hagedorn (NPH) insulin.

2 Drug Information

2.1 Drug

Generic Name

Insulin Glargine

Code Name(s)

HOE901-U300

Chemical Name

21A-glycine-31B-arginine-32B-arginine human insulin (21A-glycine-30Ba-L-arginine-30Bb-L-arginine-human insulin

CAS Registry Number:

160337-95-1

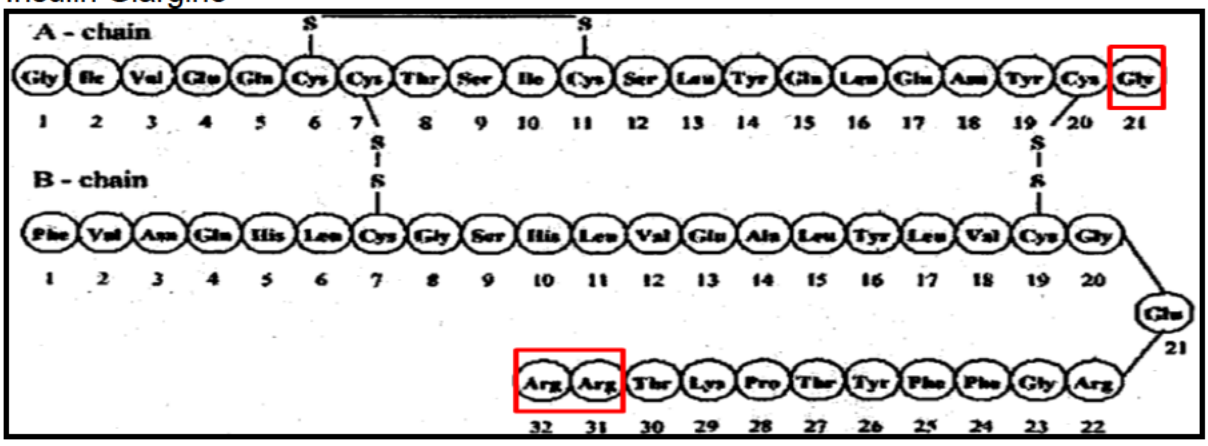
Molecular Formula/Molecular Weight

$C_{267}H_{404}N_{72}O_{78}S_6$ (606.3 amu)

Structure or Biochemical Description

Human insulin modified by the addition of 2 Arginines at positions 31 and 32 of the β-chain and the substitution of Glycine for Asparagine at position 21 of the α-chain. (b) (4)

Insulin Glargine



Pharmacologic Class

Insulin glargine is a human insulin analog produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of Escherichia coli (K12) as the production organism.

2.2 Relevant INDs, NDAs, BLAs and DMFs

Insulin glargine (Toujeo SoloStar - HOE901-U300) was developed under IND 112400. The previous formulation of insulin glargine (Lantus - HOE901-U100) was developed under IND 49078 and approved in April 2000 under NDA 21081.

2.3 Drug Formulation

Toujeo SoloStar (HOE901-U300) will be supplied as a sterile, non-pyrogen, clear, colorless, solution for injection as a 300 U/mL formulation. Insulin glargine is to be injected subcutaneously once daily.

Toujeo SoloStar (HOE901-U300) has the same composition as the current commercial formulation of insulin glargine 100 U/mL (Lantus), with adjustment of 3-times the amount of active pharmaceutical ingredient (300 U/mL insulin glargine) and corresponding zinc (b) (4) HOE901-U300 solution for injection is planned to be available as a 1.5 mL cartridge in the SoloStar pre-filled (disposable) pen.

Overview on developed formulations for insulin glargine solution for injection (cartridge)

	Insulin glargine solution for injection 300 U/mL, 1.5 mL cartridge [mg/mL]	Insulin glargine solution for injection 300 U/mL, (b) (4) cartridge (investigational use only) [mg/mL]	Commercialized insulin glargine solution for injection 100 U/mL 3 mL cartridge [mg/mL]
Insulin glargine	10.91		3.64
Zinc	(b) (4)		
Glycerol (85 per cent)			
Metacresol			
Sodium hydroxide			
Hydrochloric acid (b) (4)			
Water for injection			
1.5 mL cartridge represents the future commercial product (b) (4) cartridge represents the investigational drug product			

2.4 Comments on Novel Excipients

The excipients used in Toujeo SoloStar (HOE901-U300) were based on the commercially available formulation Lantus (HOE901-U100). The excipients are stated to be well known for parenterals and are listed in Ph. Eur. and USP.

Composition of insulin glargine solution for injection 300 U/mL in cartridges

Components [a]	Composition			Function	Reference to standards [b]
	Percentage [%]	Per mL [mg]	Per unit (1.5 mL cartridge) [mg]		
Insulin glargine *[equivalent to U (units) of insulin glargine]*	1.1	10.91 *[300]*	16.37 *[450]*	Drug substance	In-house
Metacresol [c]				(b) (4)	Ph. Eur, USP
Zinc (b) (4) [d]					Ph. Eur., USP
Glycerol (85 per cent)					Ph. Eur.
Sodium hydroxide					Ph. Eur., NF
Hydrochloric acid (b) (4) [Hydrochloric acid]					Ph. Eur., NF
Water for injection (b) (4)					Ph. Eur., USP
					Ph. Eur., NF

a Components are listed according to their pharmacopoeial names. If more than one monograph exists, other names are given in brackets, along with the compendial origin.
b Reference is made to the current edition of the Pharmacopoeia.
c For metacresol, the common chemical name "m-cresol" is also used within this document.
d (b) (4)

2.5 Comments on Impurities/Degradants of Concern

No impurities or degradation products have been specified individually as the concentrations are equal to or below the (b) (4) identification threshold when the drug product is stored as recommended. The sponsor sites that this limit is in accordance with the limits provided in the Ph. Eur. monograph "Substances for Pharmaceutical Use", where an identification threshold of > (b) (4)% and a qualification threshold of > (b) (4)% is set (b) (4)

Structural proposals for the (b) (4) major degradation products, storage (b) (4) at (b) (4) °C

RRT	Amount [area%, HPLC]	Mass	Structure
(b) (4)			

Quantities of unidentified and identified leachable and extractable impurities did not exceed (b) (4) ng/mL. Based on the (b) (4) µg/day threshold of toxicological concern (TTC), daily administration of HOE901-U300 would need to exceed (b) (4) mLs which equates to (b) (4) U of insulin glargine. Based on the concentration of insulin glargine per cartridge (450U) the toxicological risk of these impurities is negligible.

2.6 Proposed Clinical Population and Dosing Regimen

Insulin glargine is proposed to improve glycemic control in adult patients diagnosed with diabetes mellitus. Insulin glargine is formulated as a solution for subcutaneously injection and contains 10.91 mg/mL insulin glargine [equivalent to 300 U (Units) at 36.4µg/U]. The pen injector system contains the 1.5 mL cartridge and provides a maximum of 80 units in one dosing. The total content of the cartridge is 450 insulin units. The maximum initial starting dose for Lantus (HOE901-U100) was 10 I.U. [equivalent to 0.008 mg/kg/day or 0.5 mg insulin glargine per day] and is roughly equal to the proposed starting dose for Toujeo SoloStar (HOE901-U300) 0.2 Units/kg/day (0.007 mg/kg/day or 0.42 mg insulin glargine per day). Final doses will inevitably be defined by the individual insulin needs of the patient.

2.7 Regulatory Background

Sanofi's original formulation of insulin glargine (Lantus - HOE901-U100) was submitted under IND 49078 and was approved under NDA 21081. Lantus has been marketed since June 2000 in Europe and since May 2001 in the USA and other parts of the world.

The new formulation HOE901-U300 (300 U/mL) was submitted under IND 112400 in June 2011 and included a single nonclinical study comparing the local tolerance of the two insulin glargine formulations in rabbits. No additional nonclinical studies were submitted under IND 112400 or with this application. Following the August 2013 meeting the Division agreed with the sponsor's proposal to cross-reference nonclinical information previously submitted to the Lantus NDA.

During the pre-NDA meeting with the Division (October 25th 2013), the sponsor's approach to assessing the immunogenicity and CV safety of HOE901-U300 as well as the analyses and presentation of efficacy and safety results were discussed. (b) (4)

3 Studies Submitted

3.1 Studies Reviewed

Study	Route	Species	Primary Review
Primary Pharmacology			
Euglycemic Clamp Study	SC	Dog	NDA 21-081
Euglycemic Clamp Study	IV	Dog	NDA 21-081
IR Binding /pH Dependency	*In vitro*	HepG2/Skeletal Muscle/Placenta	NDA 21-081
Mitogenicity/IGF-1 Binding	*In vitro*	SaOS-2/B10 Osteosarc	NDA 21-081
IGF-1 Binding	*In vitro*	H9C2 Cardiomy Skeletal Muscle	NDA 21-081
Metabolite IR-B Binding	*In vitro*	CHO (Hu-IR-B)	NDA 21-081
Metabolite IGF-1 Binding	*In vitro*	Mouse Embryo Fibroblasts/3T3 (Hu-IGF1R)	NDA 21-081
Safety Pharmacology			
Neurological Study	SC	Mice	NDA 21-081
Cardiovascular Study	SC	Anes. Rats	NDA 21-081
Cardiovascular Study	SC	Anes. Dogs	NDA 21-081
Pulmonary Study	SC	Anes G. Pigs	NDA 21-081
Renal Study	SC	Rats	NDA 21-081
Absorption			
Bioavailability	SC	Human	NDA 21-081

Distribution			
Whole Body Radiography	IV/SC	Rats	NDA 21-081
Metabolism			
In vitro Rat	*In vitro*	Rat Adipocytes	NDA 21-081
In vivo Human	SC	Human	NDA 21-081
Elimination			
Excretion Rats	IV/SC	Rats	NDA 21-081
Excretion Dogs	IV/SC	Dogs	NDA 21-081
Toxicology			
Acute Toxicity Mice	SC	HsdWin:NMRI	NDA 21-081
Acute Toxicity Rat	SC	WISKf(SPF71)	NDA 21-081
Acute Toxicity Rat	SC	Wistar:Wiskkf	NDA 21-081
Acute Toxicity Dog	SC	Beagle	NDA 21-081
28 Day Rat	SC	Wistar:Wiskkf	NDA 21-081
3 Month Rat	SC	WISKf(SPF71)	NDA 21-081
6 Month Rat (Pivotal)	SC	Wistar:Wiskkf	NDA 21-081
12 Month Rat (Carci Pilot)	SC	Sprague-Dawley	NDA 21-081
3 Month Dog	SC	Beagle	NDA 21-081
6 Month Dog (Pivotal)	SC	Beagle	NDA 21-081
Carcinogenicity			
2 Year Mouse	SC	NMRI	NDA 21-081
2 Year Rat	SC	Sprague-Dawley	NDA 21-081
Immunotoxicology			
26 Week Immunogenicity	SC	NZW Rabbit/G. Pig	NDA 21-081
Reproductive Toxicity			
Rat Segment 1 & 2	SC	Wistar Rat	NDA 21-081
Rabbit Segment 2	SC	Himalayan Rabbit	NDA 21-081
Genotoxicity			
AMES	*in vitro*	Bacterial Strains	NDA 21-081
Chromosomal Aberration	*in vitro*	V79 Lung cell line	NDA 21-081
Chromosomal Aberration	*in vivo*	Hamster B. Marrow	NDA 21-081
HPRT Mutation Test	*In vitro*	V79 Lung cell line	NDA 21-081
Local Tolerance			
100 U vs 300 U	SC/IM/IV/PV	NZW Rabbits	IND 112400

3.2 Studies Not Reviewed

All preclinical studies submitted by Sanofi have been reviewed.

3.3 Previous Reviews Referenced

Pharmacology/Toxicology reviews under NDA 21081 (Lantus) and IND 112400 (300 IU).

4 Pharmacology

4.1 Primary Pharmacology

Insulin glargine is a human insulin analogue that facilitates blood glucose lowering through the binding and activation of specific cellular receptors (insulin and IGF-1) and is capable of initiating cell signaling comparable to the native human insulin peptide. Insulin and its analogues lower blood glucose levels by stimulating peripheral glucose uptake, especially in skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis.

(b) (4)

Insulin hexamers (b) (4) are proposed to confer the observed delayed/prolonged action of insulin glargine in humans and animals (rats, rabbits and dogs) when this molecule is neutralized in the subcutaneous space.

Insulin glargine insulin receptor (IR) binding and pH dependency were assessed in human hepatoma cells (Hep G2) and primary cultures of human skeletal muscle cells and the association/dissociation kinetics were evaluated in rat fibroblasts overexpressing the human insulin receptor. These studies revealed that insulin glargine possessed a lower binding affinity for the human insulin receptor and was a less effective activator of cellular glucose metabolism *in vitro* when compared to native human insulin (The relative binding affinity of insulin glargine is 40% lower than the native insulin peptide in the Hep G2 cell line).

Binding studies utilizing insulin receptors isolated from human placental tissue demonstrated that the affinity of insulin glargine for the IR increased as the pH moved from an alkaline environment towards neutrality. The relative receptor affinity of insulin glargine remained lower (2 to 3-fold) than the native insulin peptide over the pH range tested (pH 7 to pH 8).

The IGF-1 receptor affinity and mitogenic activity of the native insulin peptide and insulin glargine are relatively low compared to the physiological ligand (IGF-1). However, insulin glargine has a higher affinity for the IGF-1 receptor than native insulin *in vitro* demonstrated by a lower EC_{50} value for auto-phosphorylation of the IGF-1 receptor and increased thymidine incorporation in the SaOS-2/B10 (osteosarcoma) and MCF-7 (breast) cell lines. In the hepatoma HepG2 and human osteosarcoma cell lines the affinity of insulin glargine for the IGF-1 receptor is 4 to 8 times greater than that of other human insulin products (Table 1). Insulin glargine exhibited 3 to 5 times the amount of thymidine incorporation achieved with native insulin in a mitogenicity study utilizing the SaOS-2/B10 (osteosarcoma) cell line (Table 2).

The insulin glargine metabolites M1 and M2 demonstrated significantly less IGF-1 receptor binding and activation and the mitogenic activity of these metabolites in SaOS-2/B10 and MCF-7 cells was comparable to that of native insulin. Considering that therapeutic doses of insulin glargine represent total insulin glargine concentrations (including the metabolites) of 80- to 200-fold lower than the total plasma concentrations of IGF-1 and insulin glargine is rapidly metabolized to metabolite M1 *in vivo*, significant activation of IGF-1 receptors by insulin glargine and its metabolites in the clinic are improbable.

Table 1: IC_{50} Values (nM) Relative IGF-1 Receptor Binding Affinities

Test Article	Osteosarcoma Cells		Skeletal Muscle Cells		Cardiomyoblasts
	Exp #2	Exp #3	Non-diabetic	NIDDM	
Native Human Insulin	1100	6600	-	-	101
Insulin Glargine	140	470	133	431	70
M2 (Metabolite)	-	8500	-	-	
IGF-1	0.67	0.20	0.25	0.34	

Table 2: Proliferative Activity (DNA synthesis) of Insulins/IGF in Human Osteosarcoma cells

Test Article	SaOS-2/B10 Osteosarcoma Cells			
	EC_{50} (nM)		Relative Mitogenicity (%)	
	Exp #1 (n=1)	Exp #2 (n=3)	Exp #1 (n=1)	Exp #2 (n=3)
Native Human Insulin	14	3.0 ± 2.1	100	100
Native Porcine Insulin	14	-	100	-
Native Bovine Insulin	53	-	26	-
Insulin Glargine	4.8	0.6 ± 1.7	291	492
IGF-1	-	0.13	-	2308

5 Pharmacokinetics/ADME/Toxicokinetics

The pharmacokinetics, ADME and toxicokinetics of the original formulation of insulin glargine (Lantus - HOE901-U100) and its two major metabolites M1 (GlyA21-insulin) and M2 (GlyA21-des-ThrB30-insulin) were deemed acceptable under NDA 21081.

6 General Toxicology

6.1 Single-Dose Toxicity

Acute toxicity of HOE-901 (Lantus) was assessed in mice and dogs using the SC route and in rats using both the SC and IV route of administration. Acute toxicity was comparable between mice and rats regardless of the route of administration and a LD_{50} of ≥ 1000 IU was established in both species. Notable clinical signs were related directly to the onset of severe hypoglycemia and no target organs of toxicity were determined. Dogs were particular sensitive (compared to rats and mice) to the acute hypoglycemic effects incited by of insulin glargine dosing.

6.2 Repeat-Dose Toxicity

Repeat dose toxicity of subcutaneously administered HOE901-U100 (Lantus) was associated with severe hypoglycemia (exaggerated pharmacology) brought on by the relatively high insulin glargine exposures achieved in rats and dogs. The toxicology of Lantus appeared to be similar to unmodified human insulin when delivered subcutaneously to rats and dogs.

7 Genetic Toxicology

The genetic toxicity of Lantus was evaluated by three *in vitro* assays (Ames, HPRT and chromosome aberration) and in an *in vivo* micronucleus assay in Chinese hamsters. Lantus (HOE901-U100) was negative for mutagenicity and clastogenicity in all studies.

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells

Ames Assay

Lantus (HOE901-U100) was not mutagenic in the bacteria strains tested with or without exogenous metabolic activation at doses up to 50 mg/mL (5000 μg/plate).

7.2 *In Vitro* Assays in Mammalian Cells

Gene Mutations (HPRT Forward Mutation Assay) in Somatic Cell Culture (V79)

Lantus (HOE901-U100) was not mutagenic in a HPRT assay utilizing the V79 Chinese hamster lung cell line at doses ≤ 100 μg/mL in the absence or presence of metabolic activation.

Chromosome Aberration test in V79 Chinese Hamster Lung cells

Lantus (HOE901-U100) was not clastogenic in the V79 Chinese hamster lung cell line at doses ≤ 100 μg/mL in the absence or presence of metabolic activation.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Chromosome Aberration test in bone marrow cells of the Chinese Hamster

Lantus (HOE901-U100) was not clastogenic in the *in vivo* cytogenetic test in bone marrow cells isolated from Chinese Hamsters at a dose of 750 U/kg (27 mg/kg).

8 Carcinogenicity

(Mice)

The results of the 2-year carcinogenicity study in mice indicated that male mice did not have an increased risk of developing tumors when exposed to insulin glargine. Carcinogenicity data produced in female mice was deemed inconclusive due to excessive mortality observed in this gender. The tumor incidence in mice dosed with Lantus was comparable to the results of mice administered unmodified insulin.

(Rats)

The results of the 2-year carcinogenicity study in rats indicated that the vehicle (glycerol, m-cresol, pH 4.0) was inciting malignant histiocytomas at the injection site of male rats only. While the relevance of this finding to humans is unknown the current drug product Toujeo SoloStar (U300) utilizes a similar vehicle formulation (glycerol, m-cresol, pH 3.5 to 4.5) affirming the need for injection site examinations in the clinic and documentation of this finding in the label.

9 Reproductive and Developmental Toxicology

(Rats)

In a combined fertility and pre/post natal development study in Wistar rats Lantus (SC) did not produce any remarkable drug-related findings in parental fertility, F1 sexual maturation, mating and pathology at 7x (based on BSA) the 0.5 mg clinical dose.

(Rabbits)

The Segment II study in rabbits demonstrated that Lantus induced severe hypoglycemia at doses that represent approximately 2x the clinical dose. Hypoglycemia increased the incidence of abortions and fetal deaths and likely incited an increase in the incidence of ventricular dilatations (brain malformation) in fetuses. The reproductive toxicity of Lantus observed during the Segment II study was comparable to the results observed with unmodified human insulin.

10 Special Toxicology Studies

Local Tolerance

Local subcutaneous, intramuscular, intravenous and paravenous tolerance study in female rabbits (TOL1099)

Study Number, Species, Test Article(s)	Doses, Age, Weight, Route(s), Gender and Start Date
TOL1099 (GLP) Rabbits (Crl:KBL[NZW]) 300 IU HOE901/mL Batch B001 100 IU HOE901/mL Batch N413	Experimental Start Date: May 2nd 2007 Injected subcutaneous (SC, 0.1 mL), intravenous (IV, 0.5 mL), paravenous (PV, 0.1 mL) or intramuscular (IM, 0.5 mL) dose. N=6/females/group 100 IU: 6 Months Old - 3.5 kg to 5.2 kg 300 IU: 10 Months Old - 4.6 kg to 5.5 kg
Objective: To determine the local tolerability of the new 300 IU formulation in comparison to the marketed 100 IU product of HOE 901 over a 6-day test period.	
Methods: Isotonic saline solution (9 mg/mL) was injected contra-laterally as an intra-individual control in both test groups. Each rabbit was dosed either by the combination of the IM and the PV routes or the IV and the SC routes. In order to prevent the possibility of hypoglycemic shock due to treatment with insulin, rabbits were injected with 20% glucose solution (approximately 20 mL- SC) immediately and 4 hrs after administration of HOE901. Additional injection with glucose solution was provided as needed. Mortality, clinical signs and observations at injection sites were recorded daily. Body weights were measured on Days 1, 2, and 6. At necropsy (24 and 120 hrs after injection), the injection sites of 3 rabbits each were dissected, examined and fixed for histological assessment.	
Reviewer's Comments: Both the original formulation Lantus (HOE901-U100) and the new formulation Toujeo SoloStar (HOE901-U300) displayed good local tolerance in rabbits following subcutaneous injection (intended route of clinical use). Intramuscular, intravenous and paravenous injections, representing potential false routes of administration, were also well tolerated in rabbits.	

Mortality: Two rabbits (#16 and #20) from the 300 IU group died (likely due to hypoglycemia) between the last observation on Day 1 and the first observation on Day 2. Clinical signs included convulsions in these rabbits (#16 and #20) on Day 1.

Clinical Signs: Decreased activity was noted in one rabbit (#18) of the 300 IU formulation group on Day 2.

Body Weight: No significant changes in body weight were observed.

Injection Site Observations (In-Life):

100 IU HOE901/mL (Reference Formulation)

Paravenous injection:	Minimal hemorrhage/reddening and/or a minimally to moderately visible injection track was present up to Day 6 at the saline-treated injection site (4/6) and the reference formulation-treated site (5/6).
Intramuscular injection:	No abnormalities occurred.
Intravenous injection:	Minimal to moderate hemorrhage or reddening in the course of the blood vessel was present up to Day 6 a at the saline-treated injection site (5/6) and the reference formulation-treated site (6/6).
Subcutaneous injection:	A minimally visible injection track, a minimal to mild swelling or a minimal hemorrhage/reddening was present up to Day 2 at the saline-treated injection site (3/6) and the reference formulation-treated site (5/6).

300 IU HOE901/mL (New formulation - Toujeo SoloStar)

Paravenous injection:	Minimal to mild hemorrhage/reddening and a minimally to moderately visible injection track was present up to Day 6 at the saline-treated injection site (2/6) and the test formulation-treated site (6/6).
Intramuscular injection:	No abnormalities occurred.
Intravenous injection:	A minimally visible injection track, a minimal hemorrhage, or a minimal to mild reddening in the course of the blood vessel was present up to Day 6 at the saline-treated injection site (5/6) and the test formulation-treated site (6/6).
Subcutaneous injection:	A minimally visible injection track, a minimal swelling, or a minimal to mild hemorrhage/reddening was present up to Day 5 at the saline-treated injection site (4/6) and the test formulation-treated site (4/6).

Injection Site Observations (Necropsy): Macroscopic observations of the injection sites corresponding to the administration of physiological saline solution (controls) or either concentration of HOE901 were comparable (red focus/area or as white focus/area) and tended to correlated in part with the respective microscopic findings.

Microscopic Observations: Focal hemorrhage, focal necrosis and mixed inflammatory cell infiltration occurred with a similar incidence and grade of severity at injection sites corresponding to the administration of physiological saline solution (controls) or either concentration of HOE901 and there was no discernible microscopic differences between the two formulations of HOE901.

11 Integrated Summary and Safety Evaluation

The toxicological data used for the approval of Lantus (insulin glargine, 100 U/mL) supports the approval of the Toujeo SoloStar (insulin glargine, 300 U/mL) given the minor nature of change represented in the reformulated drug product.

A local tolerance study was conducted with Toujeo SoloStar (300 U/mL) as a bridge to the Lantus (100 U/mL) drug product. Both formulations of insulin glargine displayed good local tolerance in rabbits following subcutaneous injection which is the intended route of clinical use. Intramuscular, intravenous and paravenous injections, representing potential false routes of administration, were equally well tolerated in rabbits.

In Phase 1 PK/PD studies comparing Toujeo SoloStar to Lantus, Toujeo SoloStar had a flatter and more prolonged (up to 36 hrs) profile of insulin concentration and glucose-lowering activity compared to Lantus at matching doses. In Phase 3 studies, this difference in PK/PD profiles resulted in less hypoglycemia with Toujeo SoloStar compared to Lantus and suggests that Toujeo SoloStar has the potential to be safely and effectively administered up to 3 hrs before or after a patient's usual once daily injection time.

It should be noted that (b) (4) a bioequivalence study was conducted to compare drug exposure and effect between the standard cartridge formulation of Toujeo SoloStar and the formulation (b) (4) T1DM patients administered (SC) the 2 different formulations of HOE901-U300 (b) (4) in a euglycemic clamp study demonstrated bioequivalence between the standard formulation of insulin glargine 300 U/mL and the formulation (b) (4)

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01/16/2015
PT supports approval

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 206538 **Applicant: Sanofi-Aventis** **Stamp Date: April 24th 2014**

Drug Name: HOE901-U300 **NDA Type: 505(b)1**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		Cross referenced to nonclinical documents in Lantus NDA 021081
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		Insulin glargine has been registered and marketed in the U.S. since April 20, 2000 as Lantus (insulin glargine [rDNA origin] injection, 100 Units/mL) for once daily subcutaneous administration
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		HOE901-U300 has the same composition as the current commercial formulation of Lantus, with adjustment of 3-times the amount of active pharmaceutical ingredient (10.91 mg/mL = 300 U/mL insulin glargine) and corresponding zinc content (b) (4) [redacted] All excipients are stated to be: "well known, meet compendial standards, and have demonstrated compatibility with insulin glargine in various stability studies. The manufacturing process for the new HOE901-U300 will remain the same as for the approved Lantus product except for use of a 1.5 mL cartridge as primary packaging"
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		

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7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
8	Has the applicant submitted all special Studies/data requested by the Division during pre-submission discussions?	X		A local tolerance study in rabbits was submitted to bridge to Lantus and support the use of HOE901-U300 in the clinic
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		The proposed proprietary name is Toujeo SoloStar (insulin glargine U-300). Section - 13.2 - Animal Toxicology and/or Pharmacology is not represented in the label and hence human dose multiples are absent
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		No degradation products have been specified individually as all degradation products are equal to or below the (b) (4) identification threshold when the drug product is stored as recommended. Quantities of unidentified and identified leachable and extractable impurities did not exceed (b) (4) ng/mL. Based on the (b) (4) µg/day threshold of toxicological concern (TTC), daily administration of HOE901-U300 would need to exceed (b) (4) mLs which equates to (b) (4) U of insulin glargine. Based on the concentration of insulin glargine per cartridge (450U) the toxicological risk of these impurities is negligible.
11	Has the applicant addressed any abuse potential issues in the submission?		X	There has been no report of insulin glargine abuse in the clinical studies conducted with HOE901-U300.
12	If this NDA/BLA is to support an Rx to OTC switch, have all relevant studies been submitted?			Not applicable. Insulin glargine will not be marketed OTC.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __YES___X___

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Pharm/Tox does not have any review issues at this time.

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

/s/

JEFFREY A QUINN
06/12/2014

TODD M BOURCIER
06/13/2014
P/T supports filing