CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-081

CHEMISTRY REVIEW(S)

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA 21- 081 **CHEMISTRY REVIEW: #1** **DATE REVIEWED:** 29th Feb 2000

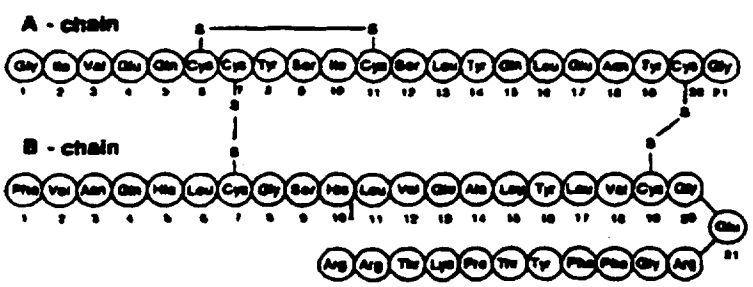
SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	9th-Apr-1999	23th Apr-1999	
Amendment	2nd-Sep-1999	3rd-Sept-1999	
Amendment	4th-Oct-1999	5th-Oct-1999	
Amendment	21st-Dec-1999	22nd-Dec-1999	
Amendment	14th-Jan-1999	14th-Jan-2000	
Amendment	28th-Feb-2000	29th-Feb-2000	

NAME & ADDRESS OF APPLICANT: Hoechst Marion Roussel, Inc.
10236 Marion Park Drive
Kansas City, MO 64134-0708

DRUG PRODUCT NAME

Proprietary:	Lantus
Nonproprietary/Established/USAusername (or equivalent):	Insulin glargine (rDNA origin)
Code Name/#:	HOE901
Chem.Type/Ther.Class:	I-S Long acting Insulin analog
ANDA Suitability Petition / DESI / Patent Status:	N/A
PHARMACOLOGICAL CATEGORY/INDICATION:	Antihyperglycemic Agent
DOSAGE FORM:	Clear aqueous solution of 100units/mL Containing 30mcg zinc, 2.7 mg m-cresol, 20 mg glycerol (85%)
STRENGTHS:	10mL, 5mL vials and 3mL cartridges that contain 100U/mL
ROUTE OF ADMINISTRATION:	Sub-cutaneous Injection
DISPENSED:	__X__ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Molecular weight: 6063 g/mol
Empirical Formula: $C_{267}H_{404}N_{72}O_{78}S_6$



SUPPORTING DOCUMENTS: DMFs —

Type/Number	Subject	Holder	Status	Review date
DMF —	—		Adequate	28th-Feb-1996
DMF —			Adequate	12th-Jan-2000
"			"	12th-Jan-2000
"			"	14th-Jan-2000
"			"	18th-Jan-2000
"			"	18th-Jan-2000

RELATED DOCUMENTS (If applicable): None

CONSULTS:

Both the Micro consult and the OptiPen device consult came in as acceptable. Refer to the CDRH consult dated 14th Sept-1999 for Optipen review. The EER summary sheet showing that all the manufacturing facilities were found acceptable has been attached at the end of the CMC review. The trade name "Lantus" and the USAN name "Insulin glargine" have been found acceptable for the drug product.

REMARKS/COMMENTS:

Lantus is the trade name for insulin glargine injection. It is a long-acting, parenteral blood-glucose –lowering agent administered subcutaneously once a day. Insulin glargine, also called HOE901, is produced by recombinant DNA technology using E.Coli bacteria — to obtain the active ingredient. Insulin glargine differs from human insulin analog in that the amino acid asparagine at position A21 is replaced by glycine and two arginines are added to the C-terminus of the B-chain. Due to the characteristics of the amino acid arginine, the isoelectric point of glargine is shifted from 5.4 to approximately 6.8 compared to human insulin, reducing the solubility of glargine at physiological pH and increasing the intermolecular bonding of the insulin hexamer. The final drug product contains 100IU/ml of insulin glargine and 30 ug/ml of zinc. It also contains 2.7 mg/ml of m-Cresol —

The primary activity of insulin glargine is to regulate of glucose metabolism. Both human insulin and insulin glargine have been shown to be equipotent in glucose-lowering effect, when given at same doses. Insulin glargine has been designed to have low solubility at neutral pH. It is completely soluble and present in solution form (at pH 4.0) before administration. After injecting into the subcutaneous tissue, the acidic solution is neutralized, leading to formation of microprecipitates from which small amounts of insulin glargine are continuously released, providing a smooth, peakless, concentration profile and a prolonged duration of action.

The host cell-vector construct of the E.Coli strain used in the production of Insulin glargine is E.coli K12 —

The information contained in the amendments submitted by the sponsor is as follows: These amendments have been reviewed and the information incorporated in the chemistry review at appropriate places.

1) 4th-Oct-1999 amendment contained CMC information about the ——— of insulin glargine injection
2) 2nd-Sept-1999 amendment contained information on validation report for insulin glargine cartridges
3) 21st-Dec-1999 amendment contained data in support of using ——— for 5 mL and 10 mL vials.
4) 14th –Jan-2000 amendment contained the sponsors responses to the CMC information request faxed to the applicant on 12th Jan-2000.

The details of manufacturing, isolation, purification and stability studies of the Insulin Glargine are provided in this submission and are the subject of this review.

CONCLUSIONS & RECOMMENDATIONS:

The chemistry, manufacturing and controls (CMC) are satisfactory and the application is approvable from Chemistry stand point.

Org. NDA # 21081

cc: HFD-510/Division File
HFD-510/PardhaK/SMooore/Rhee J
HFD-820/GibbsJ
R/D Init by: Team Leader

/S/

Komanduri Pardha, Review Chemist
filename:

/S/
3/1/2000

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
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NDA 21- 081 **Addendum to CHEMISTRY REVIEW: #1** **DATE REVIEWED:** 2nd-Mar- 2000

The following CMC comments should be communicated to the sponsor:

We remind you of your phase IV commitments specified in your submission dated 28th-Feb-2000. These commitments, along with any completion dates agreed upon, are listed below:

1) You will reevaluate the ——— for the HOE901 content, ——— ——— when the 24 month stability data on the primary stability lots of HOE901 drug substance is available.

2) You will also reevaluate the ——— ——— , related to the drug substance, when the 24-month stability data on the primary lots of HOE901 drug substance is available (May 2000).

Protocol Submission:	Submitted in the original NDA
Study Start:	The study will include stability data that you are currently collecting as well as from the data available at the end of 24-month period.
Final report submission:	As per the time frame provided in your response dt 28Th Feb-2000, ie May 2000.

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HFD-510/PardhaK/SMooore/Rhee J
HFD-820/GibbsJ
R/D Init by: Team Leader

/S/
Komanduri Pardha, Review Chemist
filename: ———

/S/
3/2/2000