CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-017
21-018

CHEMISTRY REVIEW(S)

Comments faxed 10/7/99

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

NDA #: 21-018
CHEMISTRY REVIEW #: 1 DATE REVIEWED: 7-OCT-1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE
ORIGINAL	22-DEC-1998	23-DEC-1998
AMENDMENT	4-AUG-1999	5-AUG-1999

NAME & ADDRESS OF APPLICANT: Eli Lilly and Co.
Lilly Technology Center
Indianapolis IN 46285

DRUG PRODUCT NAME
Proprietary: Pending
Established: 50% insulin lispro injection and 50% insulin lispro protamine suspension (rDNA origin)
Code Name/#:
Chem.Type/Ther.Class: 3-S

ANDA Suitability Petition / DESI / Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION: antihyperglycemic

DOSAGE FORM: injection
STRENGTHS: 100 U/ml
ROUTE OF ADMINISTRATION: sc injection
DISPENSED: X Rx ___ OTC
SPECIAL PRODUCTS: X Yes ___ No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

= Insulin Lispro under NDA 20-563

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
III	Glass vials		Adequate	24-JUL-97	
VIII	Glass vials		Adequate	29-JAN-1996	
III	Glass vials		Adequate	11-MAR-1998	
III	Rubber stoppers		Adequate	12-DEC-1997	
	Glass vials		Inadequate	27-JAN-1999	4-FEB-1999
III	Cream		Adequate	4-OCT-1999	

RELATED DOCUMENTS:

NDA 21-017

APPEARS THIS WAY
ON ORIGINAL

NDA:

CONSULTS:

Labeling and Nomenclature Committee: The committee recommended against the use of the proposed trade-name Humalog 50 (see attached reply from the committee).

Office of Post-Marketing Drug Risk Assessment: The Office under Jerry Phillips was asked to comment on the proposed trade-name Humalog Mix 50, as well as the Division's proposal to the sponsor to use the name Humalog 50/50. OPMDRA recommended against the use of the trade name Mix50. The applicant has been made aware of these recommendations, and is in the process of developing a strategy to get a trade name for the drug approved.

CDER office of Microbiology: The application was recommended for approval on the basis of assurance of sterility in the Microbiologist's review #2, dated 9-APR-1999.

REMARKS:

The applicant proposes to utilize this suspension formulation as an alternate to the approved human insulin drug product Humulin 50/50. The suspension is made of neutral protamine sulfate—insulin lispro crystals, which are long acting due to slow dissolution after sc injection. The formulation also contains 50% regular (soluble) insulin lispro, as the bolus (meal-time) fraction. As mixtures of insulin lispro and human insulin isophane exchange, the applicant developed a 'neutral protamine lispro' formulation which is functionally similar to approved (and compendial) human insulin isophane suspension. The manufacturing conditions had to be modified to optimize crystal formation, and this appears to have been successfully done. The release and shelf-life limits for 'insulin lispro in solution' for this product are outside the historical range approved for human insulin isophane suspension mixtures, however, the manufacturing and stability data provided with this application justify the applicant's proposed limits. Also, this reviewer discussed the proposed limits with the Biopharmaceutics reviewer, Dr. Mike Fossler, and was informed that the limits would, from a PD perspective, appear more than adequately tight. Therefore, this reviewer recommends that the proposed drug product shelf-life specifications be approved. The remaining tests and accept-criteria reflect those approved for the human insulin drug products. The applicant also proposes to utilize the standard and approved drug product container/closure systems, namely, 10 ml vials and 3.0 mL cartridges supplied for both re-usable and disposable insulin pen devices. Only the proposed 10 ml vial stopper is not already approved for use on the applicant's Humalog drug products. The methods validation package provided with the application is acceptable. The validation by FDA labs is not yet complete, however. The manufacturing facilities received "Acceptable" recommendations by CDER office of Compliance (see attached EES report). The labeling proposed by the applicant will need some corrections, these items will be forwarded to the Project Manager for communication to the applicant. As referred to above under "Consults", neither the trade name proposed by the applicant, nor the trade name proposed by the Division appear to be acceptable either to the LNC or the Office of post-marketing risk assessment. Therefore, the trade name for this drug remains undecided.

CONCLUSIONS & RECOMMENDATIONS:

The application is Approvable based on CMC review, pending resolution of the labeling items as well response to the request for a Phase IV commitment to re-evaluate the proposed limit of for the drug product assay and a justification of the proposed limits for 'lispro in solution' of The applicant will need to be informed of the items in the Draft Letter at the end of this review. Also, refer to the consult review of the proposed labeling by the Office of Post-Marketing Drug Risk Assessment for additional labeling comments.

/S/

William K. Berlin, Review Chemist

cc:
Org. NDA 21-018
HFD-510/Division File
HFD-510/WBerlin/date
HFD-510/CSO
HFD-510/SMoore
HFD-102/JJGibbs [#1 only]
R/D Init by: SMoore

/S/
10/18/99

filename:

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

NDA #: 21-017
CHEMISTRY REVIEW #: 2 DATE REVIEWED: 10-DEC-1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE
ORIGINAL	22-DEC-1998	23-DEC-1998
AMENDMENT	10-NOV-1999	12-NOV-1999
	22-NOV-1999	23-NOV-1999

NAME & ADDRESS OF APPLICANT:

Eli Lilly and Co.
Lilly Technology Center
Indianapolis IN 46285

DRUG PRODUCT NAME
Proprietary: Humalog Mix25/75
Established: 25% insulin lispro injection and 75% insulin lispro protamine suspension (rDNA origin)
Code Name/#:
Chem.Type/Ther.Class: 3-S

ANDA Suitability Petition / DESI / Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION: antihyperglycemic

DOSAGE FORM: injection
STRENGTHS: 100 U/ml
ROUTE OF ADMINISTRATION: sc injection
DISPENSED: X Rx ___ OTC
SPECIAL PRODUCTS: X Yes ___ No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

See Insulin Lispro under NDA 20-563

SUPPORTING DOCUMENTS:

See Chemistry Review #1.

RELATED DOCUMENTS:
NDA 21-018

NDA:
CONSULTS:
REMARKS:

The amendments dated 11-12-99 and 11-22-99 provide the response to the information requested of the firm based on Chemistry Review #1.

CONCLUSIONS & RECOMMENDATIONS:

Chemistry, manufacturing and Controls are satisfactory. With respect to chemistry, the Application can be approved.

cc:
Orig. NDA 21-017
HFD-510/Division File
HFD-510/CSO
HFD-510/SMoore

/S/ 12-10-99
Stephen Moore, Team Leader Chemist

CD Init by:

Filename:

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

NDA #: 21-018
CHEMISTRY REVIEW #: 2 DATE REVIEWED: 10-DEC-1999

UBMISSION TYPE	DOCUMENT DATE	CDER DATE
ORIGINAL	22-DEC-1998	23-DEC-1998
AMENDMENT	10-NOV-1999	12-NOV-1999
	22-NOV-1999	23-NOV-1999

NAME & ADDRESS OF APPLICANT: Eli Lilly and Co.
Lilly Technology Center
Indianapolis IN 46285

DRUG PRODUCT NAME
Proprietary: Humalog Mix50/50
Established: 50% insulin lispro injection and 50% insulin lispro protamine suspension (rDNA origin)
Code Name/#:
Chem.Type/Ther.Class: 3-S

ANDA Suitability Petition / DESI / Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION: antihyperglycemic

DOSAGE FORM: injection
STRENGTHS: 100 U/ml
ROUTE OF ADMINISTRATION: sc injection
DISPENSED: X Rx ___ OTC
SPECIAL PRODUCTS: X Yes ___ No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

ee Insulin Lispro under NDA 20-563

SUPPORTING DOCUMENTS:

See Chemistry Review #1.

RELATED DOCUMENTS:
NDA 21-017

NDA:
CONSULTS:
REMARKS:

The amendments dated 11-12-99 and 11-22-99 provide the response to the information requested of the firm based on Chemistry Review #1.

CONCLUSIONS & RECOMMENDATIONS:

Chemistry, manufacturing and Controls are satisfactory. With respect to chemistry, the Application can be approved.

cc:
Org. NDA 21-018
HFD-510/Division File
HFD-510/CSO
HFD-510/SMoore
HFD-102/JJGibbs
R/D Init by: SMoore

/S/ 12-10-99
Stephen Moore, Team Leader Chemist

Filename:

NDA 21-018 Humalog Mix 50

Date of Submission: December 21, 1998

Chemistry Review Comments

1. Please provide a Phase IV commitment to re-evaluate the lower Assay limit of [redacted] when a sufficient number of lots have been analyzed to perform a suitable statistical analysis. A limit of [redacted] appears to be more appropriate.

   Please include the following information in the commitment:
   a) Protocol Submission: Within X months following (the NDA) approval
   b) Study Start: Within Y months following approval
   c) Final Report Submission: Within Z months following approval

2. Please provide a justification for the proposed shelf-life limits for "Immediately Available Insulin Lispro" of [redacted]

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

APPEARS THIS WAY
ON ORIGINAL

Cleared for faxing by: [redacted] /ST 10/21/99
Stephen Moore, Ph.D., Chemistry Team Leader, DMEDP

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

NDA #: 21-017
CHEMISTRY REVIEW #: 1 DATE REVIEWED: 7-OCT-1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE
ORIGINAL	22-DEC-1998	23-DEC-1998
AMENDMENT	4-AUG-1999	5-AUG-1999

NAME & ADDRESS OF APPLICANT: Eli Lilly and Co.
Lilly Technology Center
Indianapolis IN 46285

DRUG PRODUCT NAME
Proprietary: Pending
Established: 25% insulin lispro injection and 75% insulin lispro protamine suspension (rDNA origin)
Code Name/#:
Chem.Type/Ther.Class: 3-S

ANDA Suitability Petition / DESI / Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION: antihyperglycemic

DOSAGE FORM: injection
STRENGTHS: 100 U/ml
ROUTE OF ADMINISTRATION: sc injection
DISPENSED: X Rx ___ OTC
SPECIAL PRODUCTS: X Yes ___ No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

ee Insulin Lispro under NDA 20-563

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
[redacted]	Glass vials	[redacted]	Adequate	24-JUL-97	
[redacted]	Glass vials		Adequate	29-JAN-1996	
[redacted]	Glass vials		Adequate	11-MAR-1998	
[redacted]	Rubber stoppers		Adequate	12-DEC-1997	
[redacted]	Glass vials		Inadequate	27-JAN-1999	4-FEB-1999
[redacted]	Cream		Adequate	4-OCT-1999	

RELATED DOCUMENTS:

NDA 21-018

APPEARS THIS WAY
ON ORIGINAL

NDA:

CONSULTS:

Labeling and Nomenclature Committee: The committee recommended against the use of the proposed trade-name Humalog Mix 25 (see attached reply from the committee).

Office of Post-Marketing Drug Risk Assessment: The Office under Jerry Phillips was asked to comment on the proposed trade-name Humalog Mix 25, as well as the Division's proposal to the sponsor to use the name Humalog 75/25. OPMDRA recommended against the use of Mix25. The applicant has been made aware of both recommendations, and is in the process of developing a strategy to get a trade name for the drug approved.

CDER office of Microbiology: The application was recommended for approval on the basis of assurance of sterility in the Microbiologist's review #2, dated 9-APR-1999.

REMARKS:

The applicant proposes to utilize this suspension formulation as an alternate to the approved human insulin drug product Humulin 70/30. The suspension is made of neutral protamine sulfate—insulin lispro crystals, which are long acting due to slow dissolution after sc injection. The formulation also contains 25% regular (soluble) insulin lispro, as the bolus (meal-time) fraction. As mixtures of insulin lispro and human insulin isophane exchange, the applicant developed a 'neutral protamine lispro' formulation which is functionally similar to approved (and compendial) human insulin isophane suspension. The manufacturing conditions had to be modified to optimize crystal formation, and this appears to have been successfully done. The release and shelf-life limits for 'insulin lispro in solution' for this product are outside the historical range approved for human insulin isophane suspension mixtures, however, the manufacturing and stability data provided with this application justify the applicant's proposed limits ( ) Also, this reviewer discussed the proposed limits with the Biopharmaceutics reviewer, Dr. Mike Fossler, and was informed that the limits would, from a PD perspective, appear more than adequately tight. Therefore, this reviewer recommends that the proposed drug product shelf-life specifications be approved. The remaining tests and accept-criteria reflect those approved for the human insulin drug products. The applicant also proposes to utilize the standard and approved drug product container/closure systems, namely, 10 ml vials and 3.0 mL cartridges supplied for both re-usable and disposable insulin pen devices. Only the proposed 10 ml vial stopper is not already approved for use on the applicant's Humalog drug products. The methods validation package provided with the application is acceptable. The validation by FDA labs is not yet complete, however. The manufacturing facilities received "Acceptable" recommendations by the CDER office of Compliance (see attached EES report). The labeling proposed by the applicant will need some corrections, and these items will be forwarded to the Project Manager for communication to the applicant. As referred to above under "Consults", neither the trade name proposed by the applicant, nor the trade name proposed by the Division appear to be acceptable either to the LNC or the Office of post-marketing risk assessment. Therefore, the trade name for this drug remains undecided.

CONCLUSIONS & RECOMMENDATIONS:

The application is Approvable based on CMC review, pending resolution of the labeling items as well response to the request for a Phase IV commitment to re-evaluate the proposed limit of for the drug product assay and a justification of the proposed limits for 'lispro in solution' of The applicant will need to be informed of the items in the Draft Letter at the end of this review. Also, refer to the consult review of the proposed labeling by the Office of Post-Marketing Drug Risk Assessment for additional labeling comments.

cc:
Org. NDA 21-017
HFD-510/Division File
HFD-510/WBerlin/date
HFD-510/CSO
HFD-510/SMoore
HFD-102/JJGibbs [#1 only]
R/D Init by: SMoore

/S/
William K. Berlin, Review Chemist

ename:

/S/
10/8/99