CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-017
21-018

CHEMISTRY REVIEW(S)
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

MISSION TYPE DOCUMENT DATE CDER DATE
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/#: 3-S
Chem Type/Ther Class:

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

PHARMACOLOGICAL CATEGORY/INDICATION: antihyperglycemic

DOSEAGE 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:

<table>
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<tr>
<th>Type/Number</th>
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</tr>
</tbody>
</table>

RELATED DOCUMENTS:
NDA 21-017

APPEARS THIS WAY ON ORIGINAL
NDA:

CONSULTS:
+ Beling 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 Mix 50. 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 neat 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 comendal) 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.

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

/S/
William K. Berlin, Review Chemist

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

NDA #: 21-017

IEMISTRY REVIEW #: 2

DATE REVIEWED: 10-DEC-1999

SUBMISSION TYPE DOCUMENT DATE CDER DATE
AMENDMENT 10-NOV-1999 12-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/#: 3-S
Chem Type/Ther Class:

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

PHARMACOLOGICAL CATEGORY/INDICATION: antihyperglycemic

DOSAGE FORM:

STRENGTHS:

ROUTE OF ADMINISTRATION: injection

DISPENSED:

SPECIAL PRODUCTS:

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

D Init by:

/s/ 12-10-99

Stephen Moore, Team Leader Chemist
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
AMENDMENT 10-NOV-1999 12-NOV-1999

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

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

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

PHARMACOLOGICAL CATEGORY/INDICATION: antihyperglycemic

DOSAGE FORM:
STRENGTHS:
ROUTE OF ADMINISTRATION:
DISPENSED:
SPECIAL PRODUCTS:
injection
100 U/ml
sc injection
X_Rx__OTC
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 21-017

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

rename:

[Signature] 12-10-99
Stephen Moore, Team Leader Chemist
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

[Signature]

Clear for faxing by: [Signature] 1/21/99

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
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DATE REVIEWED: 7-OCT-1999

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PHARMACOLOGICAL CATEGORY/INDICATION: antihyperglycemic

DOSAGE FORM: injection
STRENGTHS: 100 U/ml
ROUTE OF ADMINISTRATION: sc injection
DISPENSED:
SPECIAL PRODUCTS:

X Yes  OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
see Insulin Lispro under NDA 20-563

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RELATED DOCUMENTS:
NDA 21-018

APPEARS THIS WAY ON ORIGINAL
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 these 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.

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HFD-510/A/Berlin/date
HFD-510/CSO
HFD-510/SMoore
HFD-102/UGibbs #1 only
R/D Init by: SMoore

William K. Berlin, Review Chemist

[Signature]

10/8/99