

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

CHEMISTRY REVIEW(S)

NDA 21-919

Byetta (exenatide) Injection, 250 mcg/mL

Applicant: Amylin Pharmaceuticals, Inc.

Indication: NDA 21-919: Mono therapy to improve glycemic control in pts with type 2 diabetes.

Presentation: NDA 21-919: Prefilled pen-injector device, 60 doses of 10 mcg per dose

EA: Waiver granted

DRUG SUBSTANCE: acceptable

The **drug substance** is a 39mer peptide manufactured by Mallincrodt Tyco Health (DMF 17,114) and Bachem (DMF 17,227) (b) (4). Both of the DMFs are acceptable. Adequate controls are in place. The drug substance is adequately characterized, however it remains unclear whether the peptide is the acetate salt (b) (4) (b) (4) from the manufacturing process. Amylin has agreed to study this issue post approval and if the peptide is indeed a salt they will revise the USAN name accordingly. Impurity profiles from each manufacturer differ slightly, however they have been safety qualified in comparative toxicity studies. The specification is found acceptable. Submitted stability data support a re-test (b) (4) when stored at -20° C.

DRUG PRODUCT

The **drug product** is a buffered solution formulated with mannitol and metacresol antimicrobial preservative in glass cartridges for use in a pen injector device. Cartridge sizes are 1.2 mL and 2.4 mL for the 2 dosing regimens (combination and monotherapies). The established process controls are considered adequate. The product is manufactured by Baxter Pharmaceutical Solutions, LLC, Bloomington, IN and CP Pharmaceuticals, Ltd., Wrexham UK. The pen injectors are assembled at Eli Lilly and Company, Indianapolis, IN. The specification is acceptable and includes 2 in vitro bioassays - one functional and the

other a receptor binding assay. Controls for impurities are also adequate.

Based upon the submitted 24 months of stability data an expiry of 24 months at 5° C is granted. The stability protocol is acceptable.

All associated DMFs are acceptable.

Labeling

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/s/

Chong-Ho Kim
9/9/2008 06:39:20 AM
CHEMIST

Jim Vidra
9/9/2008 11:40:30 AM
CHEMIST

**NDA 21-773
and
NDA 21-919**

Byetta (exenatide) Injection, 250 mcg/mL

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Amylin Pharmaceuticals, Inc.

Indication: NDA 21-773: Treatment to improve glycemic control in pts with type 2 diabetes who have not achieved adequate glycemic control on metformin, a sulfonyl urea or a combination of metformin, and a sulfonyl urea.
NDA 21-919: Mono therapy to improve glycemic control in pts with type 2 diabetes.

Presentations: NDA 21-773: Prefilled pen-injector device, 60 doses of 5 mcg per dose
NDA 21-919: Prefilled pen-injector device, 60 doses of 10 mcg per dose

EER Status: acceptable 7-DEC-2004

Consults: DMETS – comments 14-FEB-2005
Statistics – comments 18-MAR-2005
Micro – approval recommendation 22-MAR-2005
EA – none – waiver granted

The Byetta NDA was submitted 29-JUN-2004

The **drug substance** is a 39mer peptide manufactured by Mallinckrodt Tyco Health (DMF 17,114) and Bachem (DMF 17,227) (b) (4). Both of the DMFs are acceptable. Adequate controls are in place. The drug substance is adequately characterized, however it remains unclear whether the peptide is the acetate salt (b) (4) from the manufacturing process. Amylin has agreed to study this issue post approval and if the peptide is indeed a salt they will revise the USAN name accordingly. Impurity profiles from each manufacturer differ slightly, however they have been safety qualified in comparative toxicity studies. The specification is found acceptable. Submitted stability data support a re-test (b) (4) when stored at -20° C.

Conclusion

Drug substance is acceptable.

The **drug product** is a buffered solution formulated with mannitol and metacresol antimicrobial preservative in glass cartridges for use in a pen injector device. Cartridge sizes are 1.2 mL and 2.4 mL for the 2 dosing regimens (combination and monotherapies). The established process controls are considered adequate. The product is manufactured by Baxter Pharmaceutical Solutions, LLC, Bloomington, IN and CP Pharmaceuticals, Ltd., Wrexham UK. The pen injectors are assembled at Eli Lilly and Company, Indianapolis, IN. The specification is acceptable and includes 2 in vitro bioassays – one functional and the other a receptor binding assay. Controls for impurities are also adequate.

Based upon the submitted 24 months of stability data an expiry of 24 months at 5° C is granted. The stability protocol is acceptable.

All associated DMFs are acceptable.

Labeling is acceptable.

Conclusion

Drug product and device are acceptable – agreements have been made to determine whether the peptide is an acetate salt and to revise the USAN name accordingly as appropriate.

Overall Conclusion

From a CMC perspective the applications are recommended for approval actions.

Eric P. Duffy, PhD
Director, DNDC II/ONDC

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/s/

Eric Duffy
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