

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208051Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

**NDA 208051
Review #1**

| | |
|-------------------------|-----------------------------|
| Drug Name/Dosage Form | NERLYNX (neratinib) Tablets |
| Strength | 40 mg |
| Route of Administration | Oral |
| Rx/OTC Dispensed | Rx |
| Applicant | Puma Biotechnology, Inc. |
| US agent, if applicable | N/A |

| SUBMISSION(S) REVIEWED | DOCUMENT DATE | DISCIPLINE(S) AFFECTED |
|----------------------------|---------------|-------------------------------------|
| Original NDA | 07/19/2016 | DS/DP/Process/Biopharm./Facility/EA |
| Labeling 0002 (3) | 7/28/2016 | DP |
| Quality Response 0008 (9) | 10/3/2016 | DS/Process/Biopharm |
| Quality Response 0035 (36) | 10/14/2016 | DS |
| Quality Response 0008 (9) | 11/3/2016 | DP |
| Quality Response 0008 (9) | 12/9/2016 | |
| Quality Response 0008 (9) | 12/20/2016 | DP |
| Quality Response 0008 (9) | 12/22/2016 | Biopharm. |
| Quality Response 0008 (9) | 1/11/2017 | Process |
| Quality Response 0008 (9) | 3/13/2017 | DP |

Quality Review Team

| DISCIPLINE | REVIEWER | BRANCH/DIVISION |
|-------------------------------------|------------------|----------------------|
| Drug Substance | Gaetan Ladouceur | CDER/OPQ/ONDP/DNDAPI |
| Drug Product | Amit Mitra | CDER/OPQ/ONDP/DNDP1 |
| Process | Huiquan Wu | CDER/OPQ/OPF/DPA1 |
| Microbiology | Huiquan Wu | CDER/OPQ/OPF/DPA1 |
| Facility | Ephrem Hunde | CDER/OPQ/OPF/DIA |
| Biopharmaceutics | Joan Zhao | CDER/OPQ/ONDP/DB |
| Regulatory Business Process Manager | Kristine Leahy | CDER/OPQ/OPRO/DRBPMI |
| Application Technical Lead | Xiao Hong Chen | CDER/OPQ/ONDP/DNDP1 |
| Laboratory (OTR) | | |



QUALITY ASSESSMENT



| | | |
|--------------------------------|-----------------|--------------------------|
| ORA Lead | Paul Perdue Jr. | ORA/OO/OMPTO/DMPTPO/MDTP |
| Environmental Analysis (EA) | Raanan Bloom | CDER/OPQ/ONDP |

APPEARS THIS WAY ON
ORIGINAL

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

| DMF # | Type | Holder | Item Referenced | Status | Date Review Completed | Comments |
|--------------|-------------|---------------|------------------------|---------------|------------------------------|--------------------|
| (b) (4) | Type III | | (b) (4) | | N/A | * See notes below. |
| | Type III | | | N/A | * See notes below. | |
| | Type III | | | N/A | * See notes below. | |
| | Type III | | | N/A | * See notes below. | |
| | Type III | | | N/A | * See notes below. | |
| | Type III | | | N/A | * See notes below. | |
| | Type III | | | N/A | * See notes below. | |
| | Type III | | | N/A | * See notes below. | |

* The manufacturing information of the individual components of the container/closure systems are referenced in the respective DMFs. The information were verified by

individual DMF cursory review. A separate review of the referenced DMFs in support of this NDA is not necessary according to the current regulatory practice.

B. Other Documents: *IND, RLD, or sister applications*

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|---|
| IND | 66783 | Initial IND was submitted on 07/31/2003 |

2. CONSULTS

| DISCIPLINE | STATUS | RECOMMENDATION | DATE | REVIEWER |
|-------------------------|--------|----------------|------|----------|
| Biostatistics | N/A | | | |
| Pharmacology/Toxicology | N/A | | | |
| CDRH | N/A | | | |
| Clinical | N/A | | | |
| Other | N/A | | | |

Executive Summary

I. Recommendations and Conclusion on Approvability

The CMC information provided in the NDA has been reviewed and found to be complete and acceptable. There are no outstanding deficiencies with the application. The NDA is recommended for **Approval** from the product quality perspective.

The following statement should be included in the action letter:

A 24 month shelf life is granted for the drug product stored as following conditions: Store at controlled room temperature, 20°C to 25°C (68°F to 77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].

II. Summary of Quality Assessments

A. Product Overview

Neratinib is a potent orally bioavailable small molecule pan-ERBB inhibitor, and is indicated for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab based therapy. Neratinib is presented as a 40-mg film-coated, orally administered, immediate release, red, film-coated tablet.

Neratinib maleate is chemically synthesized. It was initially developed by Wyeth Inc. in July 2003, and was transferred to (b) (4) in 2008, and finally Puma acquired the rights to the neratinib maleate in October 2011. Neratinib Tablets, 40-mg is an orally administered immediate-release (b) (4) tablet, red in color, film coated, oval shaped and debossed with 'W104' on one side and plain on the other side. The manufacturing process for the drug product (Neratinib Tablets, 40-mg) was initially developed by Wyeth, Inc. Throughout clinical development, both capsule and tablet dosage forms were studied. (b) (4)

. A bioequivalence study (study 3144A1-1117) was conducted which showed that the plasma pharmacokinetics of neratinib were comparable between the identical dosages of the capsule and tablet formulations.

The proposed shelf-life for Neratinib Tablets, 40-mg is 24 months.

| | |
|--|---|
| <p>Proposed Indication(s) including Intended Patient Population</p> | <p>NERLYNX is a kinase inhibitor as a single agent is indicated for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer, who have received to follow prior adjuvant trastuzumab-based</p> |
|--|---|

| | |
|--|---|
| | therapy. |
| Duration of Treatment | One year |
| Maximum Daily Dose | Recommended dose: 240 mg (6 tablets) given orally once daily with food, continuously for one year at approximately the same time every day. |
| Alternative Methods of Administration | N/A |

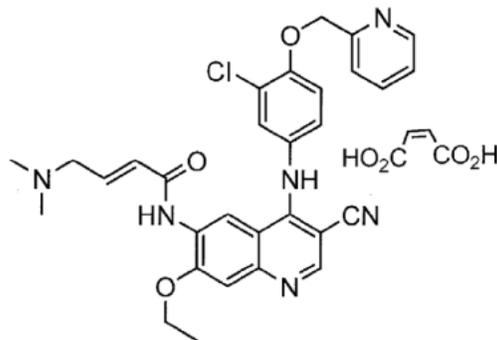
B. Quality Assessment Overview

Drug substance

- Chemical Name and Structure:

IUPAC Name: Neratinib

Structure:



Molecular Weight : 673.11 (Salt form)

Neratinib is a new molecular entity that has no chiral center and is manufactured as a maleate salt. It is slightly hygroscopic and has a very low solubility in aqueous solutions

[Redacted] (b) (4)

The current manufacturing process of neratinib maleate is performed at [Redacted] (b) (4) (Puma acquired the rights to neratinib maleate in October 2011). The synthetic process involves [Redacted] (b) (4)

[Redacted]

Validation of the drug substance manufacturing process was performed at the commercial manufacturer, (b) (4) by producing three consecutive full scale (b) (4) validation batches. The batch numbers are 16-001, 16-002, and 16-003.

There are two actual impurities observed in the finished DS (b) (4) both of which are specified impurities (limit of NMT (b) (4)% and (b) (4)% respectively). They are both class 5 (non-genotoxic) impurities. Potential organic impurities (b) (4) have not been observed at or above the reporting threshold of (b) (4)% for non-genotoxic or above the TTC for genotoxic or potentially genotoxic impurities in batches manufactured in accordance with current synthetic process.

The primary stability data obtained from an 18 months stability study showed no degradation or trends during the long term and accelerated stability studies. (b) (4)

Therefore, the proposed retest period of (b) (4) when stored in the proposed container closure system (b) (4) can be granted. (b) (4)

Drug product

Neratinib tablets, 40-mg have been developed as an orally administered, immediate-release film coated tablet. The tablet is red film coated, oval shaped, and debossed with 'W104' on one side and plain on the other side.

Each core tablet contains 40 mg neratinib (48.31 mg neratinib maleate), mannitol (b) (4) mg), microcrystalline cellulose ((b) (4) mg), crospovidone ((b) (4) mg), povidone (b) (4) ((b) (4) mg), colloidal silicon dioxide ((b) (4) mg), and magnesium stearate ((b) (4) mg). The core tablets are manufactured by a (b) (4)

The registration batch sizes are (b) (4) The proposed commercial scale is (b) (4)

The proposed commercial primary container closure system for the drug product is a 60-cc, high density polyethylene (HDPE) white opaque, round bottle with (b) (4) foil-lined induction seal, containing 180 or 126 tablets. A

(b) (4) desiccant (b) (4) is enclosed with the drug product in each container closure. The primary drug product container is packaged in a secondary carton.

The drug product quality controls are conducted with the following quality attributes: 1) Description, ID (HPLC, UV), Assay (HPLC), Uniformity of dosage units (USP<905>, Ph.Eur. 2.9.40), Chromatographic purity (HPLC), Water content (KF), Dissolution (USP apparatus 2, HPLC) and microbial limits (USP <61>).

The applicant has provided stability data for a maximum of 18 months under long term storage conditions.

The storage condition is: Store at controlled room temperature, 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. The applicant is proposing a shelf life of 24 months for the drug product. Based on satisfactory 18 months stability data under long term conditions, a 24 months tentative shelf life may be granted.

Process

(b) (4)



Facility

Drug Substance Manufacturers:

(b) (4)

Drug Product Manufacturers:

(b) (4)

Biopharmaceutics

The biopharmaceutics review evaluates the proposed dissolution method and acceptance criterion, and the need for bridging.

Based on the provided dissolution data, the following dissolution method and acceptance criterion are acceptable:

| | |
|-----------------------------|---|
| Method | USP Apparatus II (Paddle), 900 mL 0.1 N HCl (pH 12), 50 rpm |
| Acceptance Criterion | NLT (b) (4) % (Q) in 30 minutes |

No formulation bridging is needed as the proposed commercial drug product (D1005170) is the same as the phase 3 clinical batch. (b) (4)

(b) (4) From the Biopharmaceutics perspective, NDA 208051 for Nerlynx (neratinib maleate), EQ 40 mg base is recommended for approval.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

Application Technical Lead Name and Date:

Xiao Hong Chen, Ph.D.

15-Jun-2017



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Chen

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ENVIRONMENTAL ANALYSIS**R Regional Information*****Environmental Analysis***

The applicant submitted several documents in support of a claim of categorical exclusion under 21CFR25.31(b) for this application: NDA 208051: neratinib maleate, proposed for use as a single agent for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab based therapy. In support of the claim, the applicant has submitted an abbreviated Environmental Analysis, dated 6/9/2016. This document provides background information and the EIC calculations for neratinib maleate. The calculated EIC is (b) (4) ppb. This value is a worst case estimation since it assumes that all sold product is used and eliminated, no metabolism, degradation or depletion mechanisms occur, and no dilution in mixing zones. The maximum Expected Environmental Concentration (MEEC) according to FDA EA Guidelines equals (b) (4) ppb. These levels are below the level required to claim a categorical exclusion under 21CFR25.31(b).

In response to an Agency IR (December 24, 2016: email from the Regulatory Business and Process Manager, Kristine F. Leahy) the applicant has submitted (SN 0034; December 27, 2016) an Environmental Risk Assessment (ERA) previously submitted to the EMA. The ERA considers available data relating to neratinib and neratinib maleate in accordance with the Committee for Medicinal Products for Human Use (CHMP) Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMA/CHMP/SWP/4447/00, 01 June 2006).

The ERA risk profile is developed by comparison of Predicted No Effect Concentrations (PNECs) to predicted environmental concentrations. The following PNECs were calculated by the applicant based on conducted eco-toxicological studies. Compared to the EIC and/or MEEC ((b) (4) and (b) (4) ppb, respectively), this information indicates low risk to environment organisms. Based on the information provided in the ERA, extraordinary circumstances are not indicated.

The green alga NOEC of (b) (4) µg/L was considered as the endpoint for effects in surface waters. An Assessment Factor (AF) of 10 was applied.

$$PNEC_{SURFACEWATER} = NOEC/AF = (b) (4) / 10 = (b) (4) \mu g/L$$

The NOEC of (b) (4) µg/L from the Daphnia full life cycle was used to determine the groundwater PNEC. An AF of 10 was applied.

$$PNEC_{GROUNDWATER} = NOEC/AF = (b) (4) / 10 = (b) (4) \mu g/L$$

The maximum inhibitory concentration (MIC) was used to determine the PNEC for microorganisms. An AF of 10 was used.

$$\text{PNEC}_{\text{MICROORGANISMS}} = \text{MIC}/\text{AF} = \text{(b)(4)} \text{ mg/L}$$

In the early life cycle test in fathead minnows, a NOEC of $\text{(b)(4)} \mu\text{g/L}$ was the endpoint used for surface water effects. An AF of 10 was applied.

$$\text{PNEC}_{\text{SURFACEWATER}} = \text{NOEC}/\text{AF} = \text{(b)(4)}/10 = \text{(b)(4)} \mu\text{g/L}$$

Reviewer's Assessment:

The categorical exclusion cited at 21 CFR 25.31(b) is appropriate for the estimated amount of drug to be produced for direct use. Based on available information, no extraordinary circumstances are indicated. The claim of categorical exclusion is acceptable.

Primary EA Reviewer Name: Raanan A. Bloom, Ph.D.

Secondary Reviewer Name: Scott Furness, Ph.D.



Raanan
Bloom

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Michael
Furness

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LABELING

NDA 208051

R Regional Information

1.14 Labeling

1. Package Insert: Is being conducted with the labeling review. ***

(a) “Highlights” Section (21CFR 201.57(a))

| Item | Information Provided in NDA | Reviewer’s Assessment |
|--|---|-----------------------|
| Product title, Drug name (201.57(a)(2)) | | |
| Proprietary name and established name | Proprietary: Nerlynx Established Name: neratinib | Satisfactory |
| Dosage form, route of administration | Dosage: 1) Tablets Route: Oral | Satisfactory |
| Controlled drug substance symbol (if applicable) | None | N/A |
| Dosage Forms and Strengths (201.57(a)(8)) | | |
| A concise summary of dosage forms and strengths | (b) (4) | |

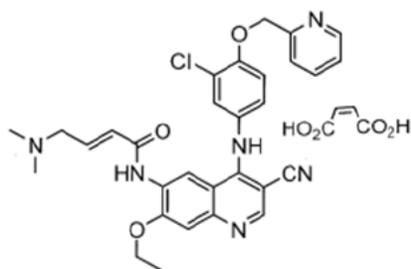
Reviewer’s Assessment: Not satisfactory. Applicant was requested to revise the established name from (b) (4) to “neratinib” in PI, SPL, container and carton label. In an amendment, dated 22-DEC-2017 the applicant recorded the requested changes.

**(b) “Full Prescribing Information” Section
3: Dosage Forms and Strengths (21CFR 201.57(c)(4))**

| Item | Information Provided in NDA | Reviewer’s Assessment |
|--|--|---|
| Available dosage forms | Tablets | Satisfactory |
| Strengths: in metric system | 40 mg | Satisfactory |
| A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable. | <p>(b) (4)</p> <p>40 mg film coated tablets that debossed with “W104” on one side and plain on the other side.</p> | <p>Change to (b) (4) (neratinib) (b) (4) 40 mg film coated tablets that debossed with “W104” on one side and plain on the other side”</p> |

#11: Description (21CFR 201.57(c)(12))

NERLYNX (neratinib (b) (4)) immediate release, film-coated tablets for oral administration contains 40 mg neratinib, equivalent to 48.31-mg of neratinib maleate. Neratinib is a member of the 4-anilino quinolidine class of protein kinase inhibitors. The molecular formula for neratinib maleate is $C_{30}H_{29}ClN_6O_3 \cdot C_4H_4O_4$ and the molecular weight is 673.11 Daltons. The chemical name is (E)-N-{4-[3-chloro-4-(pyridin-2-yl methoxy)anilino]-3-cyano-7-ethoxyquinolin-6-yl}-4-(dimethylamino)but-2-enamide maleate and its structural formula is:



Neratinib maleate is an off-white to yellow powder with pK_a s of 7.65 and 4.66. The solubility of neratinib maleate increases dramatically as neratinib becomes protonated at acidic pH. Neratinib maleate is sparingly soluble at pH 1.2 (32.90 mg/mL) and insoluble at approximate pH 5.0 and above (0.08 mg/mL).

Inactive ingredients: Tablet Core: Colloidal Silicon Dioxide, Mannitol, Microcrystalline Cellulose, Crospovidone, Povidone, Magnesium Stearate & Purified Water. Coating: (b) (4).

| Item | Information Provided in NDA | Reviewer's Assessment |
|--|--|--|
| Proprietary name and established name | Proprietary name: NERLYNX Established name: neratinib | Satisfactory |
| Dosage form and route of administration | Tablets, Oral | Satisfactory |
| Active moiety expression of strength with equivalence statement for salt (if applicable) | NERLYNX (b) (4) immediate release, film-coated tablets for oral administration | Not Satisfactory. Change to: "NERLYNX (neratinib) immediate release, film- |

| | | |
|---|---|---|
| | contain (b) (4) Neratinib is a member of the 4-anilino quinolidine class of protein kinase inhibitors” | coated tablets for oral administration contains 40 mg of neratinib, equivalent to 48.31 mg neratinib maleate. Neratinib is a member of the 4-anilino quinolidine class of protein kinase inhibitors” based on PLR |
| Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names. | See the text above under description section | Satisfactory for tablet dosage form |
| Statement of being sterile (if applicable) | N/A | N/A |
| Pharmacological/ therapeutic class | Anticancer (see label) | Satisfactory |
| Chemical name, structural formula, molecular weight | Yes | Satisfactory |
| If radioactive, statement of important nuclear characteristics. | N/A | N/A |
| Other important chemical or physical properties (such as pKa, solubility, or pH) | Yes | Satisfactory |

Reviewer’s Assessment: The applicant provided the drug substance and drug product information adequately (b) (4) According to the CFR requirement the inactive ingredients should be listed by USP/NF (established) names. The composition of excipients lists polyvinyl alcohol, USP, titanium dioxide, USP, polyethylene glycol, USP, talc, USP, and iron oxide red, USP (b) (4) These ingredients are to be listed (b) (4) on the PI. The applicant was requested to make the necessary changes in an amendment, dated 22-DEC-2017, the applicant agreed list all the components with their established names.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

NERLYNX 40 mg film-coated tablets are red, oval shaped and debossed with 'W104' on one side and plain on the other side.

(b) (4) bottle (b) (4) 180 tablets (NDC 70437-240-18).

Store at controlled room temperature, 20-25°C (68-77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].

Handling and Disposal: None included.

| Item | Information Provided in NDA | Reviewer's Assessment |
|--|--|---|
| Strength of dosage form | 40 mg film coated tablets | Satisfactory |
| Available units (e.g., bottles of 100 tablets) | 180 tablets pre bottle | Satisfactory |
| Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number | NDC number is provided | Debossing, oval shape, color coating and NDC number provided. |
| Special handling (e.g., protect from light, do not freeze) | (b) (4) | Satisfactory |
| Storage conditions | Store at controlled room temperature, 20-25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. | Satisfactory |

Manufacturer/distributor name listed at the end of PI, following Section #17

| Item | Information Provided in NDA | Reviewer's Assessment |
|---|---|-----------------------|
| Manufacturer/distributor name (21 CFR 201.1) | Distributor's name and address included: Puma Biotechnology Inc., 10880 Wilshire Blvd., Suite 2150, Los Angeles, CA 80024-4106. | Satisfactory |

Conclusion: Satisfactory (This section may be revised according to PLR).

2. Labels**1) Immediate Container Label**

40 mg neratinib tablets



Reviewer's Assessment:

The applicant provided the following required items: Established name, dose strength with salt equivalency statement, route of administration, reference to prescribing information for dosing and administration, prescription only, [REDACTED] (b) (4) [REDACTED] lot #, and expiration date. DMEPA may have additional comments. These items were included in the revised mock up. The mock up for 126 count is not included here since other than the tablet count everything else is the same for the label.

APPEARS THIS WAY
ON ORIGINAL

| Item | Comments on the Information Provided in NDA | Conclusions |
|--|--|--|
| Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2)) | Proprietary name: Nerlynx Established name: Not satisfactory | Established name is recommended to be: "neratinib" (b) (4) |
| Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4)) | Salt equivalency statement not provided in the original submission. IR sent to the applicant. The applicant made the necessary change. | Satisfactory after revision |
| Net contents (21 CFR 201.51(a)) | None | Satisfactory |
| Lot number per 21 CFR 201.18 | None | Satisfactory |
| Expiration date per 21 CFR 201.17 | None | Satisfactory |
| "Rx only" statement per 21 CFR 201.100(b)(1) | None | Satisfactory |
| Storage | None | Satisfactory |
| NDC number (per 21 CFR 201.2) (requested, but not required for all labels or | None | Satisfactory |
| Bar Code per 21 CFR 201.25(c)(2)** | None | Satisfactory |
| Name of manufacturer/distributor | None | Satisfactory |
| Others | | |

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Reviewer's Assessment: The applicant was requested to change the established name from [REDACTED] ^{(b) (4)} to "neratinib". Based on the salt equivalency guidance, it is recommended that that the statement be changed from "Each tablet contains [REDACTED] ^{(b) (4)} to "Each tablet contains 40 mg neratinib equivalent to 48.31 mg neratinib maleate". The statement "Nerlynx [REDACTED] ^{(b) (4)} tablets" be changed to "Nerlynx (neratinib) tablets, [REDACTED] ^{(b) (4)}". In an amendment, dated 19-APR-2017, to the NDA, the applicant agreed and revised the label.

2) Cartons

(b) (4)

| Item | Comments on the Information Provided in NDA | Conclusions |
|---|--|---------------------------------------|
| Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)) | Nerlynx Established name: Not satisfactory | See immediate container label comment |
| Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4)) | None | Satisfactory |
| Net contents (21 CFR 201.51(a)) | None | Satisfactory |
| Lot number per 21 CFR 201.18 | None | Satisfactory |
| Expiration date per 21 CFR 201.17 | None | Satisfactory |
| Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)] | Not satisfactory, (b) (4) the components (b) (4) is to be listed with the established name per 201.10 (a). | See comments in the PI. |
| Sterility Information (if applicable) | N/A | Satisfactory |
| "Rx only" statement per 21 CFR 201.100(b)(1) | None | Satisfactory |
| Storage Conditions | None | Satisfactory |

| | | |
|---|------------|---------------|
| NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling). also see 21 | None | Satisfactory |
| Bar Code per 21 CFR 201.25(c)(2)** | None | Satisfactory |
| Name of manufacturer/distributor | None | Satisfactory |
| “See package insert for dosage information” (21 CFR 201.55) | Referenced | Satisfactory |
| “Keep out of reach of children” (optional for Rx, required for OTC) | None | Satisfactory |
| Route of Administration (not required for oral, 21 CFR 201.100(b)(3)) | None | Satisfactory. |

Reviewer’s Assessment:

The applicant was requested to change the established name from (b) (4) to “neratinib”. Based on the salt equivalency guidance, it is recommended that that the statement be changed from “Each tablet contains (b) (4) (b) (4) to “Each tablet contains 40 mg neratinib equivalent to 48.31 mg neratinib maleate”. The statement “Nerlynx (b) (4) tablets” be changed to “Nerlynx (neratinib) tablets (b) (4)”. In an amendment, dated 19-APR-2017 the applicant revised the carton statement satisfactorily. The mock up for 126 count is not included here since other than the tablet count everything else is the same for the label.

List of Deficiencies:None

Primary Labeling Reviewer Name and Date: Amit K. Mitra, Ph.D/

Secondary Reviewer Name and Date: Anamitro Banerjee, Ph.D/



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BIOPHARMACEUTICS

Product Background:

NDA: 208051-ORIG-1

Drug Product Name / Strength: Nerlynx (Neratinib Maleate) Tablets, Eq 40 mg base

Route of Administration: Oral

Applicant Name: Puma Biotechnology, Inc.

Review Summary:

Nerlynx is proposed as a single agent for extended adjuvant therapy of HER2+ breast cancer with prior adjuvant trastuzumab-based therapy.

The drug substance, neratinib maleate, is a weakly basic molecule with pH-dependent aqueous solubility. The proposed commercial formulation is an immediate-release tablet.

This review evaluates the proposed dissolution method and acceptance criterion, and the need for bridging.

Based on the provided dissolution data, the following dissolution method and acceptance criterion are acceptable:

| | |
|-----------------------------|---|
| Method | USP Apparatus II (Paddle), 900 mL 0.1 N HCl (pH 12), 50 rpm |
| Acceptance Criterion | NLT ^(b) / ₍₄₎ % (Q) in 30 minutes |

No formulation bridging is needed as the proposed commercial drug product (D1005170) is the same as the phase 3 clinical batch.

Review Recommendation:

From the Biopharmaceutics perspective, NDA 208051 for Nerlynx (neratinib maleate), EQ 40 mg base is recommended for **APPROVAL**.

List of Submissions reviewed (table):

| Submission Type (#) | Submission(s) Reviewed | Document Date |
|----------------------------|-------------------------------|----------------------|
| NDA 208051 | Original Submission | 07/19/2016 |
| | Amendment | 10/3/2016 |

Highlight of Key Outstanding Issues from Last Cycle: N/A (First cycle)

Concise Description of Outstanding Issues: None

Drug Substance Solubility:

The solubility of neratinib maleate increases dramatically as neratinib becomes protonated at acidic pH.

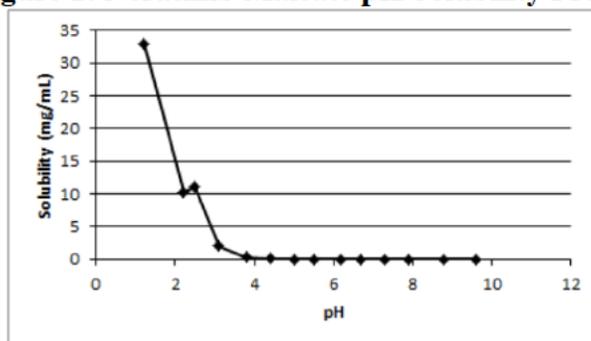
Table 1: Solubility of Neratinib Maleate in Aqueous Media as a Function of pH at 37°C

| Buffer | Solution pH ^a | Solubility mg/mL ^a | Solubility Description ^b |
|-------------------------------|--------------------------|-------------------------------|-------------------------------------|
| Potassium chloride | 1.2 | 32.90 | Sparingly soluble |
| Potassium chloride | 2.1 | 10.32 | Sparingly soluble |
| Potassium Biphthalate | 2.5 | 11.04 | Sparingly soluble |
| Potassium Biphthalate | 3.1 | 2.01 | Slightly soluble |
| Potassium Biphthalate | 3.8 | 0.53 | Very slightly soluble |
| Potassium Biphthalate | 4.4 | 0.08 | Practically insoluble |
| Potassium Biphthalate | 5.0 | BAL | Insoluble |
| Potassium Biphthalate | 5.5 | BAL | Insoluble |
| Potassium phosphate monobasic | 6.3 | BAL | Insoluble |
| Potassium phosphate monobasic | 6.7 | BAL | Insoluble |
| Potassium phosphate monobasic | 7.3 | BAL | Insoluble |
| Potassium Dihydrogenphosphate | 7.9 | BAL | Insoluble |
| Boric acid/Potassium chloride | 8.8 | BAL | Insoluble |
| Boric acid/Potassium chloride | 9.6 | BAL | Insoluble |

BAL = Below accuracy limit of the analytical method

^a pH and Solubility after 24 hours at 37°C

^b USP terminology

Figure 1: Neratinib Maleate pH Solubility Profile

The maximum solubility of neratinib maleate is 32.90 mg/mL at pH 1.2 and falls below the accuracy of the analytical method (0.08 mg/mL) at approximately pH 5.0 and above.

Permeability: Low

Drug Substance

Neratinib maleate drug substance (DS) is an-off-white to yellow powder, a weakly basic molecule with pH-dependent aqueous solubility. The calculated pKa values are 7.65 and 4.66.

**Formulation:**

The 40-mg tablet formulation (D1005170) proposed for commercialization is an immediate-release, red film coated, oval shaped tablet; this formulation was used in Phase 3 clinical studies

¹ In the firm's response (10/3/2016) to the CMC Process reviewer's IR request

and in the registration/stability program. The drug product is manufactured and coated using (b) (4) film coating process.

Table 4: Composition of Neratinib 40-mg Tablets (Formulation D1005170)

| Ingredient | Reference to Standards ^a | Function | Input/Tablet, (mg) | Input/Tablet, % (w/w) |
|---|-------------------------------------|----------|--------------------|-----------------------|
| <i>Tablet Core</i> | | | | |
| Neratinib Maleate ^b | In-house | DS | 48.31 ^c | (b) (4) |
| Mannitol | USP, Ph. Eur., JP | (b) (4) | (b) (4) | (b) (4) |
| Microcrystalline Cellulose (b) (4) | NF, Ph. Eur., JP | (b) (4) | (b) (4) | (b) (4) |
| Croscopovidone (b) (4) | NF, Ph. Eur., JP | (b) (4) | (b) (4) | (b) (4) |
| Povidone (b) (4) | USP, Ph. Eur., JP | (b) (4) | (b) (4) | (b) (4) |
| Colloidal Silicon Dioxide | NF, Ph. Eur., JP | (b) (4) | (b) (4) | (b) (4) |
| Magnesium Stearate (b) (4) | NF, Ph. Eur., JP | (b) (4) | (b) (4) | (b) (4) |
| Purified Water | USP, Ph. Eur., JP | (b) (4) | (b) (4) | (b) (4) |
| Total Weight of Tablet Core | | | | |
| <i>Film Coating</i> | | | | |
| (b) (4) | In-house | (b) (4) | (b) (4) | (b) (4) |
| (b) (4) | USP, Ph. Eur., JP | (b) (4) | (b) (4) | (b) (4) |
| Total Weight of Coated Tablet | | | | |
| Abbreviations: DS = drug substance; JP = Japanese Pharmacopoeia; NA = not applicable; NF = National Formulary; Ph. Eur. = European Pharmacopoeia; (b) (4) USP = United States Pharmacopoeia | | | | |
| ^a Where multiple compendia are listed, the compendium applied is specific to the applicable region of the submission | | | | |
| ^b (b) (4) | | | | |
| ^c 48.31 mg of neratinib maleate is stoichiometrically equivalent to 40.00 mg of neratinib free base. (b) (4) | | | | |
| (b) (4) | | | | |

Source: 3.2.P.1 Description and Composition of the Drug Product, Table 1

Dissolution Method:

The Applicant's proposed dissolution method testing conditions are summarized as follows:

| | |
|-------------------------------|--------------------|
| USP Apparatus type | USP II (Paddle) |
| Rotation (rpm) | 50 RPM |
| Medium | 0.1 N HCl (pH 1.2) |
| Volume (mL) | 900 mL |
| Temperature | 37±0.5 °C |
| Proposed Sampling Time | 30 minutes |
| Analysis Method | HPLC UV at 266 nm |

Dissolution method development was conducted in parallel with formulation and process development of the current 40-mg drug product. The method was found acceptable by Dr. Minerva Hughes in IND 66783 Submission # 0697².

Apparatus:

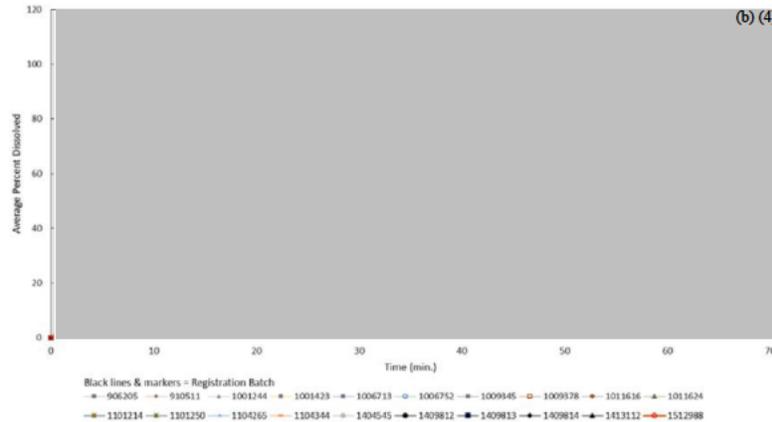
USP Apparatus 2 (paddles) with 900 mL media volume at 37.0 ± 0.5°C was selected for the dissolution development studies. Paddles were selected (b) (4) to ensure sufficient media agitation during the dissolution test.

² DARRTS: IND-66783, REV-QUALBIOPHARM-21 (Primary Review), final date 04/23/2014

Dissolution Acceptance Criteria:

Dissolution profiles of the clinical and registration stability batches at release are presented in Figure 5.

Figure 5: Dissolution Profiles of Neratinib Tablets, 40-mg Clinical and Registration Batches at Release (900 ml 0.1 N HCl, Paddles, 50 RPM, UV Detection)



Note: The four registration batches are designated in black. The 20- and 25-minute dissolution results are only available for the most recent clinical batches (1404545 and 1512988) and the four registration batches (1409812, 1409813, 1409814, and 1413112)³.

Dissolution of tablets in 0.1N HCl is rapid, with approximately (b) (4) % dissolved at 15 minutes and approximately (b) (4) % dissolved after 45 min. The Applicant stated that the initial dissolution acceptance criterion was set as Q = (b) (4) % at (b) (4) minutes for the clinical batches and proposes the acceptance criterion of NLT (b) (4) % in 30 minutes for the current proposed dissolution method.

Reviewer’s Assessment of the revised dissolution acceptance criterion: ACCEPTABLE

Application of dissolution/IVIVC in QbD

The Applicant provided its IVIVC report RPT-74654⁴. (b) (4)

³ During the course of development, time-course studies have been performed at all release and stability time points. The early batches were evaluated at the 15-, 30-, 45-, and 60- minute time points. Starting with clinical batch 1404545, all subsequent manufactured batches were evaluated on release and stability at 10-, 15-, 20-, 25-, 30-, 45- and 60- minute time points.

⁴ <\\cdsesub1\evsprod\nda208051\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\74654\rpt-74654.pdf>

Reviewer’s Assessment:

We found the IVIVC model proposed by the sponsor not acceptable due to:

(b) (4)

Bridging of Formulations

The 40-mg tablet formulation (D1005170) proposed for commercialization was used in Phase 3 clinical studies and in the stability program.

Table 6: Neratinib tablets Phase 2 and Phase 3 Formulation Composition

| Formulation | | Phase 2 (Formulation # D1005168) | | Phase 3 (Formulation # D1005170) | | | |
|-----------------------------------|----------|--------------------------------------|---------|--|---------|--|---------|
| Ingredient | Function | Early Phase 1 and 2 Clinical Studies | | Clinical Studies (including Pivotal Phase 3 Study) | | Registration and Proposed Commercial Batches | |
| | | (mg) | % (w/w) | (mg) | % (w/w) | (mg) | % (w/w) |
| <i>Tablet Core</i> | | | | | | | |
| Neratinib Maleate ^a | DS | 48.31 ^{b,c} | (b) (4) | 48.31 ^{b,d} | (b) (4) | 48.31 ^{b,d} | (b) (4) |
| Mannitol | (b) (4) | | | | | | |
| Microcrystalline Cellulose | (b) (4) | | | | | | |
| Crospovidone | (b) (4) | | | | | | |
| Povidone | (b) (4) | | | | | | |
| Colloidal Silicon Dioxide | | | | | | | |
| Magnesium Stearate | (b) (4) | | | | | | |
| Purified Water | | | | | | | |
| Total Core Tablet Weight | | | | | | | |
| <i>Film Coating</i> | | | | | | | |
| Total Coated Tablet Weight | | | | | | | |

^a (b) (4) NA = Not applicable; DS = Drug Substance

^b 48.31 mg of neratinib maleate is stoichiometrically equivalent to 40.00 mg of neratinib free base.

(b) (4)

Seventeen clinical batches and four registration stability batches were manufactured using the proposed commercial manufacturing equipment and process.

Table 7: Manufacturing Process and Equipment used for Development and Proposed Commercial Manufacturing

(b) (4)



Reviewer’s Assessment:

No formulation bridging is needed.

Biowaiver Request

Reviewer’s Assessment:

N/A. The Applicant is seeking approval for only one dosage strength, 40 mg.

R Regional Information

Comparability Protocols

Reviewer’s Assessment: No comparability protocols have been submitted.

Post-Approval Commitments

Reviewer’s Assessment: N/A

Lifecycle Management Considerations: N/A

List of Deficiencies:

None

Recommendation: From the Biopharmaceutics perspective, NDA 208051 for Nerlynx (Neratinib maleate) is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date: Zhuojun Joan Zhao, Ph.D. 3/12/2017

Secondary Reviewer Name and Date: Okpo Eradiri, Ph.D. 03/23/2017

APPENDIX I: BA STUDY 3144A1-1109

The strengths, dosage forms, and batch numbers of neratinib are summarized in Table below.

Table 8: Study Medication Information

| Drug Product | Strength (mg) | Dosage Form | Batch Number |
|--------------|----------------|-----------------|--------------|
| Neratinib | 240 mg | Tablet [slow] | 2007B0151 |
| Neratinib | 240 mg | Tablet [target] | 2007B0150 |
| Neratinib | 80 mg | Capsule | 2006B0298 |
| Neratinib | 240 mg | Powder | 2007B0141 |
| Diluent | Not Applicable | Not Applicable | 2007B0143 |

The results demonstrated that the neratinib TR 2007B0150 (b) (4), SR, and SOLN formulations were bioequivalent to the CAPS formulation 2006B0298 (b) (4).

Table 9: Statistical Comparison of Treatments Following Single Oral Dose of Neratinib 240 mg Capsule, Target Tablet, Slow-Release Table, and Solution in Healthy Subjects Under Fed Conditions

| PK Stats: Statistical Comparison for a (Single-Dose) Crossover Design | | | | | | | | | |
|---|--|--------------------------|--------------------------|--------------------------------|-------------------|----------------|-------------------|--------------------------|-----------------------------|
| Factor | p-Values from Log-Transformed Analysis of Variance | | | | | | | | |
| | C _{max} (ng/mL) | t _{max} (hr) | t _{1/2} (hr) | AUC _T (ng*hr/mL) | AUC (ng*hr/mL) | CL/F (L/hr) | CL/F (L/hr/kg) | V _Z /F (L) | V _Z /F (L/kg) |
| Period | 0.206 | 0.116 | 0.567 | 0.628 | 0.743 | 0.743 | 0.751 | 0.605 | 0.588 |
| Seq | 0.658 | 0.736 | 0.158 | 0.348 | 0.329 | 0.329 | 0.466 | 0.596 | 0.663 |
| Treatment | 0.907 | 0.030 | 0.790 | 0.245 | 0.336 | 0.336 | 0.335 | 0.150 | 0.150 |
| Pair-wise Comparison: 240 mg TR (Test) vs. 3 × 80 mg caps (Ref) | | | | | | | | | |
| Ratio of Least Square Geometric Means (%) | 99 | | | 95 | 95 | | | | |
| 90% Confidence Interval around Ratio | 89-109 | | | 90-101 | 90-101 | | | | |
| Probability < 80% | <0.001 | | | <0.001 | <0.001 | | | | |
| Probability > 125% | <0.001 | | | <0.001 | <0.001 | | | | |
| Statistical Power | 98.3 | | | 100.0 | 100.0 | | | | |
| Pair-wise Comparison: 240 mg SR (Test) vs. 3 × 80 mg caps (Ref) | | | | | | | | | |
| Ratio of Least Square Geometric Means (%) | 101 | | | 96 | 96 | | | | |
| 90% Confidence Interval around Ratio | 92-111 | | | 90-102 | 90-101 | | | | |
| Probability < 80% | <0.001 | | | <0.001 | <0.001 | | | | |
| Probability > 125% | <0.001 | | | <0.001 | <0.001 | | | | |
| Statistical Power | 98.2 | | | 100.0 | 100.0 | | | | |
| Pair-wise Comparison: 240 mg SOLN (Test) vs. 3 × 80 mg caps (Ref) | | | | | | | | | |
| Ratio of Least Square Geometric Means (%) | 103 | | | 101 | 100 | | | | |
| 90% Confidence Interval around Ratio | 93-113 | | | 95-107 | 94-106 | | | | |
| Probability < 80% | <0.001 | | | <0.001 | <0.001 | | | | |
| Probability > 125% | <0.001 | | | <0.001 | <0.001 | | | | |
| Statistical Power | 98.2 | | | 100.0 | 100.0 | | | | |

Appendix II: BA Study 3144A1-1117

The strengths, dosage forms, and batch numbers of neratinib used in the study are summarized in Table below.

Table 10: Neratinib Batch Information

| Drug Product | Strength (mg) | Dosage Form | Formulation Number | |
|--------------|---------------|-------------|--------------------|--------------|
| | | | (Stock Number) | Batch Number |
| Neratinib | 40 | Tablet | 0932762C | 811521 |
| Neratinib | 240 | Tablet | 0932763C | 812001 |
| Neratinib | 80 | Capsule | 0932256V | 2008B0026 |

The results showed that the one 240-mg tablet Batch 812001 (b) (4) and six 40-mg tablets batch 811521 (b) (4) formulations of neratinib were bioequivalent to each other and to the three 80-mg capsule formulation batch 2008B0026 (b) (4).

Table 11: Statistical Comparison of Treatments Following a Single Oral Dose of One 240-mg Tablet, Six 40-mg Tablets, and Three 80-mg Capsules in Healthy Subjects Under Fed Conditions: Study 3144A1-1117-US

| Statistical Comparison for a (Single-Dose) Crossover Design | | | |
|---|-----------------------------|-------------------------------|------------------|
| p-Values From Log-Transformed Analysis of Variance | | | |
| Factor | C _{max} (ng/mL) | AUC _T (ng•h/mL) | AUC (ng•h/mL) |
| Period | <0.05 | 0.295 | 0.386 |
| Sequence | 0.848 | 0.955 | 0.934 |
| Treatment | 0.350 | 0.937 | 0.899 |
| Intersubject CV% | 34.9 | 28.8 | 28.7 |
| Intrasubject CV% | 16.2 | 15.5 | 15.4 |
| Pairwise Comparison: Neratinib One 240-mg Tablet (Test) Versus Neratinib Three 80-mg Capsules (Reference) | | | |
| Ratio of Least Square Geometric Means (%) | 107 | 99 | 99 |
| 90% Confidence Interval Around Ratio | 99-117 | 92-108 | 91-107 |
| Probability <80% | 0.00000370 | 0.0000266 | 0.0000338 |
| Probability >125% | 0.00209 | 0.0000127 | 0.00000742 |
| Total Probability (<80%, >125%) | 0.00209 | 0.0000394 | 0.0000412 |
| Statistical Power (%) | 99.6 | 99.8 | 99.8 |
| Pairwise Comparison: Neratinib Six 40-mg Tablets (Test) Versus Neratinib Three 80-mg Capsules (Reference) | | | |
| Ratio of Least Square Geometric Means (%) | 102 | 101 | 101 |
| 90% Confidence Interval Around Ratio | 94-112 | 93-110 | 93-110 |
| Probability <80% | 0.0000109 | 0.0000126 | 0.0000116 |
| Probability >125% | 0.000181 | 0.0000522 | 0.0000426 |
| Total Probability (<80%, >125%) | 0.000192 | 0.0000648 | 0.0000541 |
| Statistical Power (%) | 99.5 | 99.7 | 99.7 |
| Pairwise Comparison: Neratinib Six 40-mg Tablets (Test) Versus Neratinib one 240-mg Tablets (Reference) | | | |
| Ratio of Least Square Geometric Means (%) | 95 | 102 | 102 |
| 90% Confidence Interval Around Ratio | 88-104 | 94-110 | 94-111 |
| Probability <80% | 0.000599 | 0.00000669 | 0.00000416 |
| Probability >125% | 0.00000183 | 0.0000595 | 0.0000706 |
| Total Probability (<80%, >125%) | 0.000601 | 0.0000662 | 0.0000748 |
| Statistical Power (%) | 99.6 | 99.7 | 99.8 |

Appendix III Target and Slow Tablet

Table 12: Comparison of Neratinib Tablet “Target” and “Slow” Tablet Core Formulations

| Component | Function | Tablet Core “Target” Formulation ^a | Tablet Core “Slow” Formulation |
|----------------------------|----------------|--|-----------------------------------|
| (b) (4) | | | |
| Neratinib maleate | Drug Substance | | (b) (4) |
| Mannitol USP | (b) (4) | | (b) (4) |
| Microcrystalline Cellulose | | | (b) (4) |
| Crospovidone | | | (b) (4) |
| Povidone | (b) (4) | | (b) (4) |
| Colloidal Silicon Dioxide | | | (b) (4) |
| Purified Water | | | (b) (4) |
| | | | |
| Magnesium Stearate | | | (b) (4) |
| <i>Coating</i> | | | |
| | | (b) (4) | |
| | | N/A | N/A |
| | | N/A | N/A |
| Tablet Core Weight | | | (b) (4) |
| | | | |
| (b) (4) | | | |



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