

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208051Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
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Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
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Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	June 13, 2017
Subject	Review to determine if a REMS is necessary
Established Name	Neratinib
Trade Name	Nerlynx
Name of Applicant	Puma Biotechnology, Inc.
Therapeutic Class	Kinase Inhibitor
Formulation(s)	40 mg tablets
Dosing Regimen	240 mg (6 tablets) given orally once daily with food, continuously for one year at approximately the same time every day

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity neratinib (Nerlynx) is necessary to ensure the benefits outweigh its risks. Puma Biotechnology, Inc. submitted a New Drug Application (NDA) 208051 for neratinib with the proposed indication for the extended adjuvant treatment of adult patients with early-stage human epidermal growth factor receptor (HER2)-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab based therapy. The serious risks associated with the use of neratinib are diarrhea (grade ≥ 3 diarrhea) and hepatotoxicity. The applicant did not submit a REMS with this application but proposed Prescribing Information that includes Warnings and Precautions, as well as information to be included in section 17, Patient Information.

DRISK and the Division of Oncology Products I (DOP I) agree that a REMS is not necessary to ensure the benefits outweigh the risks of neratinib. The current standard of care for patients with HER2-positive breast cancer patients is treatment with chemotherapy and one year of adjuvant trastuzumab; however, up to 20% of those patients have recurrent disease. Therefore, there remains a clear medical need to develop new therapies for the treatment of early breast cancer to extend life, delay disease progression and/or lessen breast cancer related symptoms. If approved, neratinib will provide an option where there are currently no approved therapies which improve upon the benefits of trastuzumab for HER2-positive patients in the adjuvant setting. The most concerning adverse reactions associated with the use of neratinib are diarrhea (grade ≥ 3) and hepatotoxicity. These adverse events were considered reversible either with dose reduction or dose discontinuation; additionally, diarrhea can be managed with antidiarrheal prophylaxis recommended in the label. The risks of diarrhea and hepatotoxicity will be communicated in the Warnings and Precautions section of the product label; dose modifications for diarrhea, as well as antidiarrheal prophylaxis dosing regimens will also be included in labeling.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) neratinib (Nerlynx) is necessary to ensure the benefits outweigh its risks. Puma Biotechnology, Inc. submitted a New Drug Application (NDA) 208051 for neratinib with the proposed indication for the extended adjuvant treatment of adult patients with early-stage human epidermal growth factor receptor (HER2)-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab based therapy.¹ This application is under review in the DOP I. The serious risks associated with the use of neratinib are diarrhea (grade ≥ 3 diarrhea) and hepatotoxicity. The applicant did not submit a REMS with this application but proposed Prescribing Information that includes warnings and precautions and a Patient Information section to address the risks of diarrhea and hepatotoxicity.

2 Background

2.1 PRODUCT INFORMATION

Neratinib is a new molecular entity (NME) NDA in the 505(b)(1) pathway.^a It is a kinase inhibitor proposed for the indication of extended adjuvant treatment of adult patients with early-stage human

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

epidermal growth factor receptor (HER2)-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab based therapy. Neratinib irreversibly binds to Epidermal Growth Factor Receptor (EGFR), Human Epidermal Growth Factor Receptor 2 (HER2), and HER4. In vitro, neratinib reduces EGFR and HER2 autophosphorylation, downstream mitogen-activated protein kinases (MAPK) and protein kinase B (Akt) signaling pathways, and showed antitumor activity in EGFR and/or HER2-expressing carcinoma cell lines. Neratinib human metabolites M3, M6, M7 and M11 inhibited the activity of EGFR, HER2 and HER4 in vitro. In vivo, oral administration of neratinib inhibited tumor growth in mouse xenograft models with tumor cell lines expressing HER2 and EGFR. ² Neratinib is prepared as 40mg tablets to be taken by the oral route. The proposed dose of neratinib is 240 mg (6 tablets) given orally once daily with food, continuously for one year at approximately the same time every day.^b Neratinib is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for neratinib (NDA 208051) relevant to this review:

- 07/01/2003: Investigation New Drug (IND) 066783 submission was received from Wyeth.
- 10/06/2009: Wyeth transferred IND sponsorship to Pfizer (Wyeth was maintained as wholly owned subsidiary of Pfizer)
- 03/18/2009: FDA denied a request by Wyatt for a Special Protocol Assessment, as efficacy and safety had not been established in patients with metastatic breast cancer
- 06/10/2009: Wyeth submitted Study 3004 (ExteNET) to the IND.
- 04/30/2012: Pfizer transferred IND sponsorship to Puma, following licensing from Pfizer
-  (b) (4)
- 10/14/2012: FDA agreed with the applicants initial pediatric study plan and acknowledged the request for a full waiver from PREA requirements.
- 03/21/2016: Pre-NDA meeting with Puma – FDA advised they did not encourage an NDA submission based on the efficacy and safety results of Study 3004. This was due to several study conduct issues which would make interpretation of the results problematic. The Applicant was advised that if an NDA was submitted, an Oncologic Drugs Advisory Committee discussion would be required.
- 07/19/2016: NDA 208051 submission for neratinib with the proposed indication for the extended adjuvant treatment of adult patients with early-stage human epidermal growth factor receptor (HER2)-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab based therapy, received.
- 12/15/2016: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that all major safety concerns can be addressed through review of the submission and the responses to the agency's information requests.

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- 05/24/2017: The Oncologic Drugs Advisory Committee (ODAC) was convened to discuss the risk-benefit profile of neratinib for extended adjuvant therapy in an early and often curative disease setting. The AC voted 12-4 to recommend approval of neratinib for the extended adjuvant treatment of adult patients with early-stage ERBB2-positive breast cancer who have received prior adjuvant trastuzumab-based therapy, but shared the concern that the proposed indication for extended adjuvant treatment in HER2-positive breast cancer is overly broad given the unfavorable subgroup results in the pivotal trial. A REMS proposal was not discussed.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Breast cancer is the second leading cause of cancer death in women.^c The chance that a woman will die from breast cancer is about 1 in 37 (about 2.7%). The American Cancer Society estimates that approximately 252,710 new cases of invasive breast cancer will be diagnosed in women in United States,^d and about 40,610 women will die from breast cancer in 2017.³ Breast cancer is a molecularly diverse disease with several clearly defined molecular subgroups.⁴ Clinically, however, three therapeutic groups are used: those classified as hormone receptor-positive, those classified as HER2-positive, and those classified as triple-negative. The predominant subset is HR-positive, HER2-negative disease. Of the new breast cancer cases diagnosed worldwide each year, roughly 60% to 65% are HR-positive, 20% to 25% are HER2-positive, and 15% to 18% are triple-negative.^{5,6} HER 2 protein overexpression or gene amplification in breast cancer tumors is associated with more aggressive clinical disease and poorer prognosis.⁷ The expression profile of biological markers in breast cancer is correlated with prognosis and response to treatment, and therefore plays an important role in treatment decisions.⁸

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The current standard of care for patients with HER2-positive early breast cancer is chemotherapy and one year of adjuvant trastuzumab.⁹ Pertuzumab is also used in combination with trastuzumab and docetaxel as neoadjuvant treatment for selected patients. Lapatinib plus trastuzumab improves outcomes for metastatic HER2-positive breast cancer and increases the pathologic complete response in the neoadjuvant setting, but their role as adjuvant therapy remains uncertain. Adjuvant treatment that includes lapatinib did not significantly improve DFS compared with trastuzumab alone and added toxicity. One year of adjuvant trastuzumab remains the standard of care.¹⁰ (see Table 1 in the Appendix). Approximately 20% of patients with HER2-positive early breast cancer will recur within 5 years after adjuvant therapy. Patients with more high-risk disease features are at greater risk for recurrence.^{11,12} There are currently no approved therapies which improve upon the benefits of trastuzumab for HER2-positive patients in the adjuvant setting.¹³

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

4 Benefit Assessment

The pivotal trial, ExteNET (study 3004) supporting this application consisted of a multicenter, randomized, double-blind, placebo-controlled trial of one year of neratinib versus placebo in women with early stage HER2 overexpressed/amplified breast cancer after adjuvant treatment with trastuzumab. A total of 2840 patients with early-stage HER2-positive breast cancer 1-2 years after completing treatment with adjuvant trastuzumab were randomized to receive either neratinib (n=1420) or placebo (n=1420). Randomization was stratified by the following factors: Hormonal status; nodal status (0, 1-3 vs 4 or more positive nodes) and whether trastuzumab was given sequentially versus concurrently with chemotherapy. The median age was 52 years (60% were ≥ 50 years old, 12% were ≥ 65 years old); 81% were Caucasian, 3% black or African American, 14% Asian and 3% other. Neratinib 240 mg or placebo were given orally once daily for one year.

The major efficacy outcome measure was invasive disease-free survival (iDFS), which is defined as the time between the date of randomization to the first occurrence of invasive recurrence (local/regional, ipsilateral or contralateral breast cancer), distant recurrence, or death from any cause, with 2 years and 28 days of follow-up. The efficacy results from ExteNET trial are summarized in Table 2.¹ A total of 173 iDFS events were observed, consisting of 67 (4.7%) events on the neratinib arm and 106 (7.5%) events on the placebo arm. A statistically significant difference favoring neratinib was observed with a stratified hazard ratio of 0.66 (95% CI: 0.49, 0.90) and two-sided stratified log-rank test (p-value = 0.008).^e The estimated absolute difference in iDFS rates at 2-years was 2.3% (94.2% on the neratinib arm compared to 91.9% on the placebo arm).^{13,14}

Table 2: Primary Analysis of Disease-free Survival, ITT Population¹

Population	Number of Events/ Total N (%)		KM Estimate for iDFS at 24 months (% , 95% CI)		Stratified HR (95% CI)	p-value
	Neratinib	Placebo	Neratinib	Placebo		
ITT	67/1420 (4.7)	106/1420 (7.5)	94.2 (92.6, 95.4)	91.9 (90.2, 93.2)	0.66 (0.49, 0.90)	0.008

The Oncology Drugs Advisory Committee (ODAC) Meeting was convened on May 24, 2017 to discuss the risk-benefit profile of neratinib for extended adjuvant therapy in an early and often curative disease setting. After hearing presentations on efficacy and safety from the applicant and the FDA, the ODAC voted 12 yes, 4 no to the following voting question: Given the totality of evidence, is the risk-benefit profile of neratinib sufficient to support treatment in the proposed population?¹³ The AC voted 12-4 to recommend approval of neratinib for the extended adjuvant treatment of adult patients with early-stage ERBB2-positive breast cancer who have received prior adjuvant trastuzumab-based therapy, but shared the concern that the proposed indication for extended adjuvant treatment in HER2-positive breast cancer is overly broad given the unfavorable subgroup results in the pivotal trial.

^e Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

During the development of neratinib, the ownership of the product changed hands and there were unplanned amendments and potential uncertainty introduced with respect to the magnitude of neratinib effect. However, based on the sensitivity analyses conducted, the results appear to be generally similar to the primary analysis results, supporting an effect of neratinib.¹³ FDA clinical reviewers stated that while it is uncertain which patients derive the greatest benefit from a year of extended adjuvant therapy with neratinib, the overall 2.3% improvement in iDFS at 2 years is considered clinically meaningful in carefully selected patients.¹⁴

5 Risk Assessment & Safe-Use Conditions

At the time of this writing, labeling negotiations were still ongoing with the Sponsor. The following section is a summary of relevant safety information to date for neratinib. The safety analysis of neratinib primarily focuses on 2,816 patients treated on Study 3004 (1,408 patients treated with neratinib and 1,408 patients treated with placebo). Results from Study 6201 (PUMA-NER-6201), an ongoing Phase 2 study investigating the incidence and severity of diarrhea in patients treated with antidiarrheal prophylaxis given during the first two 28-day treatment cycles of neratinib, were also analyzed. The median duration of treatment was 11.6 months in the neratinib arm and 11.8 months in the placebo arm.¹ Adverse events were assessed during the treatment period and for 28 days after the last dose of study drug. The most common ($\geq 20\%$) adverse reactions with neratinib are diarrhea, nausea, abdominal pain, fatigue, and vomiting.

Of the 1,408 patients receiving neratinib in Study 3004, 388 (27.6%) experienced an adverse reaction that resulted in permanent discontinuation; the most common adverse reactions leading to discontinuation were diarrhea (16.8%), vomiting (3.8%), and nausea (2.8%). Adverse events leading to dose interruptions occurred in 629 (44.7%) of patients receiving neratinib; the most common were again diarrhea (33.9%), vomiting (5.4%), and nausea (5.4%). Adverse events leading to dose reduction occurred in 440 (31.3%) of patients; the most common were diarrhea (26.4%), nausea (2.8%), and abdominal pain (1.6%).¹³

Serious Adverse Reactions

Nonfatal serious adverse events occurred in 7.3% of patients on the neratinib arm and 6.0% of patients on the placebo arm in Study 3004.¹³ The most frequent treatment-related SAE was diarrhea with 22 (1.6%) patients on the neratinib arm and 1 (0.1%) patient on the placebo arm. Serious adverse reactions reported ≥ 5 neratinib-treated patients arm compared with the placebo-treated patients included diarrhea (1.6% vs. 0.1%), vomiting (0.9% vs. 0.1%), dehydration (0.6% vs. 0.1%), cellulitis (0.4% vs. 0.1%), renal failure (0.4% vs. 0%), and erysipelas (0.4% vs. 0%).¹

Serious risks associated with the use of neratinib are diarrhea (grade ≥ 3), hepatotoxicity, and embryo-fetal toxicity; if approved, these risks will be communicated in the Warnings and Precaution section of the label.^f

^f Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

5.1 DIARRHEA

Diarrhea was the most frequently reported adverse reaction in the neratinib arm with an overall incidence of 95% (vs. 35% compared to placebo arm) and 40% of patients experiencing at least one episode of Grade 3 diarrhea (vs. 1.6% compared to placebo arm). Grade 4 diarrhea occurred in 0.1% of neratinib-treated patients (vs. 0% to placebo arm). In Study 3004, 28% of patients discontinued neratinib due to an adverse event (AE) in neratinib-treated arm compared to 5% in placebo arm, and the most common AE leading to discontinuation was diarrhea (16.8%) in neratinib arm vs. 0.2% in placebo arm. In Study 3004, the proportion of patients who had a dose reduction due treatment-emergent diarrhea was 26.4% in the neratinib group and 0.6% in the placebo group; a similar trend was observed for dose hold (33.9%, neratinib; 1.8%, placebo). Diarrhea was reported as most frequent treatment-related SAE in Study 3004 with 22 (1.6%) patients on the neratinib arm and 1 (0.1%) patient on the placebo arm. All diarrhea related SAEs in the neratinib arm were reversible after discontinuation of study drug. The median time to first onset of Grade \geq 3 diarrhea was 8 days (range, 1-350). The median cumulative duration of Grade \geq 3 diarrhea was 5 days (range, 1-139). The majority of patients had diarrhea in the first month of treatment; generally, the number of patients with diarrhea decreased with time from the start of treatment.

The risk of diarrhea will be communicated in the Warnings and Precautions in label. Dose modifications for diarrhea and antidiarrheal prophylaxis dosing regimens will be included in the Dosage and Administration section of the label.

5.2 HEPATOTOXICITY

Neratinib has been associated with hepatotoxicity characterized by increased liver enzymes. In Study 3004, the incidence of Grade 3 treatment-emergent adverse events (TEAEs) of hepatic toxicity was 22 (1.6%) patients in the neratinib group (vs. 7 (0.5%) patients in the placebo arm). Grade 4 events were reported in 3 (0.2%) patients in the neratinib arm and 1 (0.1%) patient in the placebo group. The Grade 4 adverse events of alanine aminotransferase increased and aspartate aminotransferase increased were resolved upon discontinuation of neratinib. In Study 3004, 74 (5.3%) patients experienced an AST or ALT increase \geq 3 x ULN compared to 20 (1.4%) patients in placebo arm, and 24 (1.7%) patients experienced an AST or ALT elevation $>$ 5 x ULN compared to 9 (0.6%) patients in placebo arm (\geq Grade 3). Hepatotoxicity or increases in liver transaminases led to drug discontinuation in 24 (1.7%) neratinib-treated patients compared to 3 (0.2%) placebo-treated patients.^{15,1}

Six patients (0.43%) in the neratinib group compared to 2 patients (0.14%) met the biochemical definition of Hy's law; one patient experienced aminotransferase and bilirubin elevations assessed as being probably caused by neratinib. Study treatment was permanently discontinued in this patient and the event resolved.

The risk of hepatotoxicity, including recommendations for monitoring, will be communicated in the Warnings and Precautions of the label.

5.3 EMBRYO-FETAL TOXICITY

Based on findings from animal studies and its mechanism of action, neratinib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of neratinib to

pregnant rabbits during organogenesis caused abortions, embryo-fetal death and fetal abnormalities in rabbits at maternal AUCs approximately 0.2 times the AUC in patients receiving the recommended dose.

The risk of embryo-fetal toxicity will be communicated in the Warnings and Precautions section of the label.

6 Expected Postmarket Use

The proposed indication is for the extended adjuvant treatment of adult patients with early-stage human epidermal growth factor receptor (HER2)-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab based therapy. It is expected that oncologists will be the primary health care providers to prescribe neratinib and the use will be in the outpatient setting.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for neratinib beyond routine pharmacovigilance and labeling. They do propose a Patient Information section as part of labeling to inform patients regarding the potential risks of diarrhea and hepatotoxicity.

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for neratinib, DRISK considers patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and prescribing population.

Based on the efficacy and safety information currently available, the clinical reviewers recommend approval of neratinib for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer to follow adjuvant trastuzumab-based therapy.

AEs typically observed with EGFR TKIs (eg, lapatinib, erlotinib, gefitinib, afatinib, vandetanib) include GI, dermatologic, and hepatic toxicities. EGFR-directed tyrosine kinase inhibitors are associated with high frequencies of clinically important diarrhea, and depending on the agent, up to 95% of patients may experience some grade of diarrhea, although the risk of grade 3/4 events tends to be lower (<15%).¹⁶ The most concerning adverse reactions associated with the use of neratinib are diarrhea (grade ≥ 3) and hepatotoxicity. These adverse events were considered reversible either with dose reduction or dose discontinuation; additionally, diarrhea can be managed with antidiarrheal prophylaxis recommended in the label.

DRISK and DOP-1 have determined that if approved, a REMS is not necessary to ensure the benefits of neratinib outweigh its risks. Labeling including a Warnings and Precautions, Patient Information section will be used to communicate the safety issues associated with neratinib. The adverse events of diarrhea and hepatotoxicity will be included in the Warnings and Precautions section of the label, and dose modifications for diarrhea and antidiarrheal prophylaxis dosing regimens will be included in the Dosage and Administration section of the label. At this time, none of these risks will receive a boxed warning in the label.

A REMS is not necessary to ensure the benefits outweigh the risks of neratinib for the following reasons: both primary and secondary efficacy outcomes appear to be generally in favor of the neratinib arm. Albeit the current standard of care for patients with HER2-positive early breast cancer is chemotherapy and one year of adjuvant trastuzumab, approximately 20% of patients with HER2-positive early breast cancer will recur within 5 years. Patients with more high-risk disease features are at greater risk for recurrence. There are currently no approved therapies which improve upon the benefits of trastuzumab for HER2-positive patients in the adjuvant setting. In light of the high burden of disease, there remains a clear medical need to develop new therapies for the treatment of early breast cancer to extend life, delay disease progression and/or lessen breast cancer related symptoms. The safety profile of neratinib is acceptable for the intended population. The risk of diarrhea and hepatotoxicity will be communicated in labeling in the Warnings and Precautions section of the label and an antidiarrheal prophylaxis regimen will be included in the label.

9 Conclusion & Recommendations

If approved, DRISK has determined that a REMS is not necessary to ensure the benefits outweigh its risks. The management of the risks associated with neratinib treatment can be communicated through labeling. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 TABLE 1: SUMMARY OF TREATMENT OPTIONS RELEVANT TO PROPOSED INDICATION

Trade Name (Generic)	Approved year	Indication	Dosing/ Administration	Warnings and Precautions	REMS
Herceptin ¹⁷ (trastuzumab)	1998	Adjuvant Treatment of HER2-Overexpressing Breast Cancer	<ul style="list-style-type: none"> Initial dose of 4 mg/kg over 90 minute IV infusion, then 2 mg/kg over 30 minute IV infusion weekly for 12 weeks (with paclitaxel or docetaxel) or 18 weeks (with docetaxel/carboplatin). One week after the last weekly dose of Herceptin, administer 6 mg/kg as an IV infusion over 30–90 minutes every three weeks to complete a total of 52 weeks of therapy, or Initial dose of 8 mg/kg over 90 minutes IV infusion, then 6 mg/kg over 30–90 minutes IV infusion every three weeks for 52 weeks. 	<p>Boxed Warning for Cardiomyopathy, Infusion Reactions, Pulmonary Toxicity, and Embryo-Fetal Toxicity.</p> <p>Exacerbation of Chemotherapy-Induced Neutropenia</p>	No REMS
Kadcyla ¹⁸ (ado-trastuzumab emtansine)	2013	indicated, as a single agent, for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: <ul style="list-style-type: none"> Received prior therapy for metastatic disease, or 	3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity	<p>Boxed Warning for Hepatotoxicity, Left Ventricular Dysfunction, and Embryo-Fetal Toxicity.</p> <p>Pulmonary Toxicity, Infusion-Related Reactions, Hypersensitivity Reactions, Hemorrhage,</p>	No REMS

		<ul style="list-style-type: none"> Developed disease recurrence during or within six months of completing adjuvant therapy. 		Thrombocytopenia, Neurotoxicity	
Perjeta (pertuzumab)	2012	<ul style="list-style-type: none"> Use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. Use in combination with trastuzumab and docetaxel as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer 	<p>The initial PERJETA dose is 840 mg administered as a 60-minute intravenous infusion, followed every 3 weeks thereafter by 420 mg administered as a 30 to 60 minute intravenous infusion.</p> <ul style="list-style-type: none"> MBC: Administer PERJETA, trastuzumab, and docetaxel by intravenous infusion every 3 weeks. Neoadjuvant: Administer PERJETA, trastuzumab, and docetaxel by intravenous infusion preoperatively every 3 weeks for 3 to 6 cycles. 	<p>Boxed Warning for Left Ventricular Dysfunction, and Embryo-Fetal Toxicity.</p> <p>Infusion-Related Reactions, Hypersensitivity Reactions/Anaphylaxis</p>	No REMS
Tykerb (lapatinib)	2007	Indicated in combination with capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.	1,250 mg (5 tablets) given orally once daily on Days 1-21 continuously in combination with capecitabine 2,000 mg/m ² /day (administered orally in 2 doses approximately 12 hours apart) on Days 1-14 in a repeating 21 day cycle.	Decreased Left Ventricular Ejection Fraction, Dose reductions for Patients with Severe Hepatic Impairment, Diarrhea, QT Prolongation, Fetal harm	No REMS

11 References

¹ Proposed Prescribing Information for neratinib as currently edited by the FDA, last updated June 9, 2017.

² Puma Biotechnology, Inc. Clinical Overview for Neratinib, dated July 19, 2016.

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- ¹⁴ Singh H, Walker A. DOP1 Multidisciplinary Clinical Review (draft) for NDA 208051 neratinib, dated June 13, 2017.
- ¹⁵ Puma Biotechnology, Inc. Summary of Clinical Safety for neratinib, dated July 19, 2016.
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- ¹⁷ Herceptin. Prescribing Information (last updated 04/2017).
- ¹⁸ Kadcyła. Prescribing Information (last updated 07/2016).

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