

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125427Orig1s000

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

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: January 14, 2013

Reviewer(s): Suzanne Robottom, Pharm.D.
Division of Risk Management (DRISK)

Team Leader: Cynthia LaCivita, Pharm.D.
DRISK

Division Director: Claudia Manzo, Pharm.D.
DRISK

Subject: Review evaluates if a risk evaluation and mitigation strategy (REMS) is needed

Drug Name(s): xxx-Trastuzumab emtansine (Kadcyla)
(modification to the established name is under discussion)

Therapeutic Class: HER2-directed antibody and microtubule inhibitor conjugate

Dosage and Route: 3.6 mg/kg IV every 3 weeks

Application Type/Number: BLA 125427

Applicant/sponsor: Genentech, Inc.

OSE RCM #: 2012-1570

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for xxx-trastuzumab emtansine. The applicant did not submit a proposed REMS or risk management plan.

1.1 BACKGROUND

xxx-Trastuzumab emtansine is proposed as a single agent for the treatment of patients with HER-2 positive, (b)(4) metastatic breast cancer who have received prior treatment with trastuzumab and a taxane.

xxx-Trastuzumab emtansine is an antibody-drug conjugate. Trastuzumab is a humanized monoclonal IgG1 antibody that selectively binds to HER2. It inhibits the proliferation of human tumor cells that overexpress HER2. In this product, trastuzumab is linked to emtansine, a microtubule inhibitory mytansinoid that is cytotoxic by inhibiting tubulin polymerization. The emtansine allows intracellular drug delivery specifically to HER2-overexpressing cells.¹

xxx-Trastuzumab emtansine is formulated as a lyophilized powder in 100 mg and 160 mg single use vials. The recommended dose is 3.6 mg/kg given as an intravenous infusion every 3 weeks until disease progression or unacceptable toxicity.

1.2 OTHER PRODUCTS IN THE SAME THERAPEUTIC CLASS/THERAPEUTIC ALTERNATIVES

There are two approved monoclonal antibodies that target HER2, Herceptin (trastuzumab; approved 1998) and Perjeta (pertuzumab; approved 2012) and indicated for the treatment of metastatic breast cancer.²

The phase 3 clinical trial submitted for approval of xxx-trastuzumab emtansine, compared xxx-trastuzumab emtansine to combination treatment with Tykerb (lapatinib) and Xeloda (capecitabine).

1.2.1 Known Adverse Events

The professional labeling for Herceptin and Perjeta include the following Warnings and Precautions:

¹ Verma S, et al. Trastuzumab emtansine for HER2-Positive Advanced Breast Cancer. NEJM 2012; 367:1783-1791.

² **Herceptin** approved indication relating to metastatic breast cancer: in combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer; as a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease. **Perjeta** approved indication: for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

| | <u>Herceptin</u> | <u>Perjeta</u> |
|--|----------------------|----------------------|
| Cardiomyopathy / Left ventricular dysfunction | Yes + Boxed Warning | Yes |
| Infusion Reactions | Yes+ Boxed Warning | Yes |
| Pulmonary Toxicity | Yes + Boxed Warning | Yes |
| Embryo-Fetal Toxicity | Yes + Boxed Warning | Yes + Boxed Warning |
| | Pregnancy Category D | Pregnancy Category D |
| Exacerbation of chemotherapy-induced neutropenia | Yes | No |
| HER2 testing | Yes | Yes |

Tykerb (lapatinib) is a tyrosine kinase inhibitor. The professional labeling for lapatinib includes a Boxed Warning for hepatotoxicity and the following risks listed in the Warnings and Precautions section:

- Decreased left ventricular ejection fraction
- Diarrhea
- Interstitial lung disease/pneumonitis
- QT prolongation
- Embryo-fetal harm

Tykerb is pregnancy category D.

Xeloda (capecitabine) is a nucleoside metabolic inhibitor. The professional labeling for capecitabine includes a Boxed Warning for increased risk of bleeding/coagulopathies due to capecitabine -warfarin drug interaction. The following risks are listed in the Warnings and Precautions section:

- Diarrhea
- Cardiotoxicity
- Dihydropyrimidine dehydrogenase deficiency
- Renal insufficiency
- Pregnancy
- Hand-and-Foot syndrome
- Hyperbilirubinemia
- Hematologic events
- Hepatic insufficiency
- Fetal harm

Xeloda is pregnancy category D.

None of these products have a REMS to address the serious safety concerns associated with these products.

2 MATERIALS REVIEWED

- Midcycle meeting slides. November 6, 2012.

- Herceptin [package insert]. South San Francisco, CA: Genentech, Inc.;2010.
- Perjeta [package insert]. South San Francisco, CA: Genentech, Inc.;2012.
- Tykerb [package insert].
- Xeloda [package insert]. South San Francisco, CA: Genentech, Inc.;2011.
- Abdus-Samad J. Proprietary Name Review. Signed in DARRTS by Bridges T, Taylor K and Holquist C on November 6, 2012.

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

Please refer to the clinical review by Dr. Laleh Amiri-Kordestani for the full review of efficacy.

The efficacy of xxx-trastuzumab emtansine was evaluated in a randomized, multicenter, open-label trial of 991 patients. The co-primary end points were progression free survival (PFS; reviewed by independent radiologic review committee) based on tumor response assessments and overall survival (OS). The xxx-trastuzumab emtansine treatment group had improved/increased median PFS of 9.6 months (vs 6.4 months in capecitabine/lapatinib arm) and 30.9 months OS (vs 25.1 months in capecitabine/lapatinib arm). Both endpoints were statistically significant.

3.2 SAFETY CONCERNS

Please refer to the clinical review by Dr. Gideon Blumenthal for the full review of the safety. The following is a summary of the key findings from clinical presentation at the midcycle meeting on November 6, 2012 and the FDA draft labeling sent to the sponsor on December 26, 2012.

The following risks are included in the Warnings section of the FDA draft labeling:



(b) (4)

The FDA draft label includes cardiac toxicity as a **Boxed Warning** consistent with Herceptin.

(b) (4)

In summary, the following table (presented at the midcycle meeting) provides an overview of the serious adverse experienced in patients treated with xxx-trastuzumab emtansine in comparison to lapatinib/capecitabine.

| | xxx-Trastuzumab Emtansine (N=490) | Lapatinib/ Capecitabine (N=488) |
|---|--|--|
| AE Grade \geq 3 | 40.8% | 57% |
| Death due to Gr 5 AE (<30 days) | 1 (0.2%) | 4 (0.8%) |

4 DISCUSSION

Largely, the risks identified with xxx-trastuzumab emtansine treatment are consistent with other approved chemotherapeutic agents. More specifically, cardiotoxicity, infusion-related reactions, pulmonary toxicity, embryo-fetal toxicity, and cytopenias are known adverse events of Herceptin, Perjeta, and other metastatic breast cancer treatments (lapatinib/capecitabine). Hepatotoxicity is addressed in a Boxed Warning for lapatinib. Neurotoxicity is not a Warning in these labels. However, neuropathies are associated with a variety of cytotoxic agents.

At the present time, FDA and the sponsor are working to negotiate a change to the established name to reduce overdosing errors resulting from product confusion.

Despite these serious adverse events, in the phase 3 clinical trial patients treated with xxx-trastuzumab emtansine overall had *fewer* grade \geq 3 adverse events than patients treated with lapatinib/capecitabine. Moreover, xxx-trastuzumab emtansine demonstrated longer PFS and OS compared to lapatinib/capecitabine.

DRISK does not recommend a REMS to address any of the risks associated with xxx-trastuzumab emtansine at this time. Based on the available data, severity of the disease, treatment alternatives and their associated toxicities, familiarity of these adverse drug events and appropriate management within the prescribing population, and the potential benefit of xxx-trastuzumab emtansine, these risks can be adequately addressed through labeling at this time. This view is shared by the Division of Oncology Products 1 (DOP1).

5 CONCLUSION

In conclusion, DRISK and DOP1 agree that a REMS is not required for xxx-trastuzumab emtansine at this time. If new safety information becomes available or use includes a new patient population, the risk-benefit of this drug should be re-evaluated.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUZANNE C BERKMAN ROBOTOM
01/14/2013

CLAUDIA B MANZO
01/14/2013
concur