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*APPLICATION NUMBER:*

**103792Orig1s5311**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

<b>Date</b>	3/7/2014
<b>From</b>	Amna Ibrahim MD
<b>Subject</b>	Division Director Summary Review
<b>NDA/BLA #</b>	103792
<b>Supplement #</b>	5311
<b>Applicant Name</b>	Herceptin
<b>Date of Submission</b>	11/25/2013
<b>PDUFA Goal Date</b>	5/28/2014
<b>Proprietary Name / Established (USAN) Name</b>	Herceptin trastuzumab
<b>Dosage Forms / Strength</b>	Intravenous/ 21 mg/ml
<b>Proposed Indication(s)</b>	1. For the treatment of HER2 overexpressing breast cancer 2. For the treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma
<b>Action/Recommended Action for NME:</b>	Approval

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review	Cortazar/Beaver
Statistical Review	Tang/Bloomquist
Pharmacology Toxicology Review	N/A
CMC Review/OBP Review	N/A
Microbiology Review	N/A
Clinical Pharmacology Review	N/A
OPDP	Toscano
DSI	N/A
CDTL Review	Cortazar
OSE/DMEPA	Abdus-Samadi
OSE/DDRE	N/A
OSE/DRISK	N/A

OND=Office of New Drugs  
 DDMAC=Division of Drug Marketing, Advertising and Communication  
 OSE= Office of Surveillance and Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DSI=Division of Scientific Investigations  
 DDRE= Division of Drug Risk Evaluation  
 DRISK=Division of Risk Management  
 CDTL=Cross-Discipline Team Leader

## 1. Introduction

Herceptin, BLA 103792, was initially approved in September 1998. This supplemental BLA has been submitted to address PMC# 1 and PMC# 3 outlined in the supplement approval letter dated November 2006. Clinical and statistical information was provided for review and to update the label.

## 2. Background

Per applicant, “The purpose of this supplemental BLA submission is to provide the FDA with efficacy and safety results from the protocol-specified preplanned final OS analysis of studies NSABP B-31 and NCCTG N9831 in fulfillment of the aforementioned PMCs # 1 and #3 and to accordingly update the USPI for Herceptin administered concurrently with the taxane component of adjuvant chemotherapy in the treatment of patients with HER2 positive (b) (4)BC.”

The PMCs were as follows:

**PMC# 1:** To provide a final study report at the time of the final analysis of overall survival (analysis based on 710 deaths) in accordance with the statistical analysis plan of April 2005 for integrated analysis of Studies NSABP B31 and NCCTG N9831. The final study report should include the primary datasets and programs for generation of analyses and all subset analyses for the final analysis of overall survival and an updated analysis of disease-free survival, including exploratory analyses in subgroups based on the timing and type of hormonal treatment administered to patients. (b) (4)

**PMC#3:** To provide interim cardiac safety updates on an annual basis beginning on 30 September 2006, as the first cutoff date and ending with a final comprehensive cardiac safety analysis report submitted by 30 September 2012. Each annual cardiac safety update will include a detailed narrative summary of each new clinical event with associated radiologic reports and laboratory findings for all patients enrolled as of the termination of study enrollment in April 2005. The first annual cardiac safety update will be submitted by 28 April 2007. The final comprehensive cardiac safety analysis will be included in the final study report based on 710 deaths. In addition, the final comprehensive study report will contain primary datasets for the ITT population and summary analyses that include, but are not limited to, the analyses described in the statistical analysis plan of April 2005 for integrated analysis of Studies NSABP B31 and NCCTG N9831.

## 3. CMC/Device

N/A

## **4. Nonclinical Pharmacology/Toxicology**

N/A

## **5. Clinical Pharmacology/Biopharmaceutics**

N/A

## **6. Clinical Microbiology**

N/A

## **7. Clinical/Statistical-Efficacy**

Please see the clinical/statistical joint review and the CDTL review for details.

Per the CDTL, Dr Cortazar, “This application jointly analyzed two randomized Phase 3 studies: The National Surgical Adjuvant Breast and Bowel Cancer Project (NSABP) Study B-31 and the North Central Cancer Treatment Group (NCCTG) Study N9831.” And that “(t)he studies were considered amenable for a joint analysis given that both contained comparable control and treatment arms and although the population in the studies differed slightly, both high-risk node-negative and node-positive patients are of high risk of recurrence and death.”

The joint analysis included 3752 women receiving adjuvant chemotherapy for HER2 overexpressing breast cancer were enrolled for adjuvant treatment. The two arms compared were doxorubicin + cyclophosphamide (AC) followed by paclitaxel (T) [AC→T] versus AC→T with Herceptin treatment continued for a total of 52 weeks [AC→T+H]. The 2006 approval was based on the 2-year follow-up of patients on these arms. The current supplement provides for a prespecified update after a median of approximately 8 years.

The final efficacy results for overall survival (OS) continue to support the superiority of trastuzumab therapy in the adjuvant setting with no new safety signals. At 8.3 years of median follow-up, the hazard ratio for OS was 0.64 (95% CI: 0.55, 0.74),  $p < 0.0001$ . The disease-free survival (DFS) results remain consistent with the DFS findings at 2.0 years of median follow-up.

## **8. Safety**

PMC #3 provided for final comprehensive cardiac safety update, a known concern for Herceptin. Per clinical statistical review as well as the CDTL review, updated safety results including cardiac toxicity, indicated no change in the risk profile of Herceptin and are consistent with prior safety reports.

## 9. Advisory Committee Meeting

None conducted

## 10. Pediatrics

N/A

## 11. Other Relevant Regulatory Issues

- Other consults: OPDP reviewed labelling and had no comments/suggestions.

There are no other unresolved /relevant regulatory issues

## 12. Labeling

Includes:

- Proprietary name: N/A
- Physician labeling: Major issues were discussed and resolved. Recommendations in the DMEPA review were incorporated in the label.
- Carton and immediate container labels: unchanged
- Patient labeling/Medication guide: none

## 13. Decision/Action/Risk Benefit Assessment

- Regulatory Action:  
Approval
- Risk Benefit Assessment  
The improvement in DFS and OS are consistent with the interim analysis which led to the initial approval for this indication. The improvement is clinically relevant and statistically significant. The safety profile remains the same as already included in the label. The risk-benefit assessment remains in favor of the Herceptin arm and remains unchanged since the previous approval.
- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None

- Recommendation for Postmarketing Requirements and Commitments

Division Director Review  
BLA 103792  
Herceptin

PMC 1 and 3 are fulfilled. There are no new PMRs and PMCs based on this supplement.

Amna Ibrahim MD  
Deputy Director  
DOP1, CDER, FDA

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/s/  
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AMNA IBRAHIM  
03/07/2014