CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-065

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-065 SUPPL # HFD # 150

Trade Name IXEMPRA (ixabepilone) for Injection

Generic Name N/A

Applicant Name Bristol-Myers Squibb Company

Approval Date, If Known October 16, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☐
		! Explain:
Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

Name of person completing form: Sharon Thomas
Title: Consumer Safety Officer
Date: October 9, 2007

Name of Office/Division Director signing form: Robert L. Justice, M.D.
Title: Division Director, Division of Drug Oncology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Robert Justice
10/12/2007 12:52:03 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # :22-065 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: April 16, 2007 **PDUFA Goal Date:** October 16, 2007

HFD 150 **Trade and generic names/dosage form:** IXEMPRA™ (ixabepilone)/ Intravenous

Applicant: Bristol-Myers Squibb Company **Therapeutic Class:** _____

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- ☑ **Yes. Please proceed to the next question.**
- **No. PREA does not apply. Skip to signature block.**

**** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.***

Indication(s) *previously approved* (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Treatment of patients with metastatic or locally advanced breast cancer.

Is this an orphan indication?

- ☐ **PREA does not apply. Skip to signature block.**
- ☑ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ☑ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☑ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- ❑ **Yes. PREA does not apply. Skip to signature block.**
- ❑ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**
- ❑ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager
Sharon Thomas

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Sharon Thomas
6/11/2007 03:14:05 PM

Bristol Myers Squibb Company

NDA NO. 22-065

IXABEPILONE (BMS-247550) FOR INJECTION

CERTIFICATION: DEBARRED PERSONS

As required by Section 306(k)(1) of the Federal Food, Drug and Cosmetics Act, Bristol-Myers Squibb Company certifies that it has not used and will not use in any capacity the services of any person listed as debarred under Section 306 (a) or (b) of the Federal Food, Drug and Cosmetics Act in connection with this Application.

A. Heather Knight-Trent

A. Heather Knight Trent, PharmD
Director Global Regulatory Science
Bristol-Myers Squibb Company
5 Research Parkway
Signature 91 Building 3SIG-3034
Wallingford, CT 06492
203-677-3858

7/13/06
Certification Date

Thomas, Sharon

From: Burbank, Linda
Sent: Wednesday, October 17, 2007 9:41 AM
To: Chelsey Kelly; Cindi Stephens; Suanna Bruinooge
Cc: Cohen, Martin H; Jones, Glen D (CDER); Pazdur, Richard; Spillman, Dianne D; Weiss, Karen
Subject: FDA approves ixabepilone for injection (IXEMPRA) for two breast cancer indications

Attachments: Ixempra Burst 10 16 07.doc

On October 16, 2007, the Division of Drug Oncology Products in FDA's Office of Oncology Drug Products (OODP) approved ixabepilone for injection (IXEMPRA™, Bristol-Myers Squibb) for the following two indications:

- Ixempra™ is indicated in combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated.

- Ixempra™ is indicated as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine.

Below is an announcement for distribution to ASCO members.

xempra Burst 10 16 07.doc (45...

Please include myself and Dianne Spillman on the distribution list when sending out the announcement.

Thanks,
Linda

Linda Burbank
Regulatory Information Specialist
Office of Oncology Drug Products
Center for Drug Evaluation & Research, FDA
Ph 301-796-1335
Fax 301-796-9909
E-mail linda.burbank@fda.hhs.gov

Appears This Way
On Original

From the American Society of Clinical Oncology.
In cooperation with the Food and Drug Administration (FDA), and as a service to our members, ASCO will periodically distribute information about newly approved therapies for cancer patients. This helps FDA to inform oncologists and professionals in oncology-related fields of recent approvals in a timely manner. Included in the email from the FDA will be a link to the product label, which will provide the relevant clinical information on the indication, contraindications, dosing, and safety. In sending this information, ASCO does not endorse any product or therapy and does not take any position on the safety or efficacy of the product or therapy described. The following is a message from the FDA's Office of Oncology Drug Products Director, Dr. Richard Pazdur:

On October 16, 2007, the U.S. Food and Drug Administration approved ixabepilone for injection (IXEMPRA™, Bristol-Myers Squibb) for the following two indications:

- Ixempra™ is indicated in combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated.

- Ixempra™ is indicated as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine.

A randomized, multinational, open-label trial of 752 patients with locally advanced or metastatic breast cancer evaluated the efficacy and safety of ixabepilone (40 mg/m^2 IV once every three weeks) plus capecitabine compared to therapy with capecitabine alone. Patients had previously received an anthracycline and a taxane, had evidence of disease progression or resistance, or, in the case of the anthracycline, received a minimum required cumulative dose. Treatment arms were balanced with regards to prior therapies, disease sites, hormone receptor status and HER2 expression. Patients receiving combination therapy had a statistically significant improvement in progression-free survival (PFS), defined as radiologic progression or death from any cause (hazard ratio 0.69, $p<0.0001$). The median PFS was 5.7 months in the combination arm and 4.1 months in the capecitabine alone arm. Patients in the combination arm also had an increased objective tumor response rate. Survival data for this trial are not yet mature.

Ixabepilone monotherapy was evaluated in a single arm trial of 126 patients with metastatic or locally advanced breast cancer who had previously received an anthracycline, a taxane and capecitabine, and who had disease progression or, in the case of the anthracycline, received a minimum required cumulative dose. Ixabepilone was administered at the same dose and schedule as in the combination trial. The objective response rate based on independent radiologic review was 12.4% (95% CI: 6.9, 19.9). The objective response rate based on investigator assessments was 18.3% (95% CI: 11.9, 26.1). The median response duration was 6.0 months (95% CI: 5.0, 7.6).

Treatment with ixabepilone caused new or worsening peripheral neuropathy in approximately 65% of patients treated. Grade 3 or 4 peripheral neuropathy occurred in 23% of patients treated with ixabepilone and capecitabine, with no grade 3 or 4 peripheral neuropathy reported in the capecitabine arm. In the ixabepilone monotherapy trial, 14% experienced grade 3 or 4 peripheral neuropathy. Neuropathy was generally reversible to Grade 1 or better with cessation of therapy.

Ixabepilone in combination with capecitabine resulted in a 68% incidence of Grade 3 or 4 neutropenia compared to 11% with capecitabine alone. Twelve patients receiving ixabepilone in combination with capecitabine died from complications arising from neutropenia. The incidence of neutropenia related deaths was higher in patients with baseline moderate or severe hepatic impairment when treated with both ixabepilone and capecitabine. This combination should not be used in patients with moderate or severe hepatic impairment. When used as monotherapy, 54% of patients treated with ixabepilone experienced Grade 3 or 4 neutropenia.

Other commonly observed toxicities (>20%) included anemia, leukopenia, thrombocytopenia, fatigue/asthenia, myalgia/arthralgia, alopecia, nausea, vomiting, stomatitis/mucositis, diarrhea, and musculoskeletal pain. The following additional reactions occurred in ≥20% in the combination treatment arm: palmar-plantar erythrodysesthesia (hand-foot) syndrome, anorexia, abdominal pain, nail disorder, and constipation.

Full prescribing information, including clinical trial information, safety, dosing, drug-drug interactions and contraindications, is available at www.fda.gov/cder/foi/label/2007/022065lbl.pdf.

"ASCO periodically e-mails its membership messages of professional interest. If you would prefer not to receive these messages, reply to this e-mail with the word REMOVE in the subject field. You will receive one additional e-mail message to confirm your removal from this e-mail list."

Thomas, Sharon

From: Mortimer, Joanne [JMortimer@coh.org]
Sent: Tuesday, October 02, 2007 6:07 PM
To: Thomas, Sharon
Subject: RE: ixabepilone: Questions and CSO responses
Attachments: Questions and Responses from Dr Mortimer (2).doc

I did make some changes.

Joanne Mortimer M.D., F.A.C.P.

Administrative Director of Phase I Programs
Associate Director for Affiliate Programs
Professor, Division of Medical Oncology & Experimental Therapeutics
City of Hope Comprehensive Cancer Center
1500 East Duarte Road
Duarte, CA 91010

626-256-HOPE (ext 61200)
626-930-5362 (FAX)

From: Thomas, Sharon [mailto:Sharon.Thomas@fda.hhs.gov]
Sent: Friday, September 28, 2007 4:10 PM
To: Mortimer, Joanne
Subject: ixabepilone: Questions and CSO responses

Dear Dr. Mortimer,

Thank you again for your participation and review of ixabepilone. It is necessary for the consultant to provide written responses to the FDA. I have attached my abbreviated written responses from the t-con you had with Dr. Lechleider and Dagher. Would it be possible for you to review and edit my responses that we may incorporate into our system? Please feel free to totally revise.

Thank you,
Sharon Thomas,CSO
<<Questions and Responses from Dr Mortimer.doc>>

"EMF <COH.org>" made the following annotations.

NDA: 22-065, Ixabepilone
October 2, 2007

Questions and Responses from Dr. Mortimer

1) Does the increase in PFS for the combination of ixabepilone with capecitabine as demonstrated in Study 046, without an as yet demonstrated improvement in OS, demonstrate a significant clinical benefit in this patient population?
    - **No. Despite an improvement in PFS, it is unlikely that there will be an improvement in OS. (Examples include doxorubicin → paclitaxel vs doxorubicin + paclitaxel)**
    - **The exception to this is Herceptin in advanced disease. Although not specifically designed as a crossover trial. 67% of women initially assigned to chemotherapy alone (compared with chemotherapy + Herceptin) subsequently received Herceptin. Yet the overall survival favors the group who received concomitant chemotherapy with Herceptin.**

2) Does the ORR for ixabepilone monotherapy as demonstrated in Study 081 and supporting studies represent a likely clinical benefit for patients who have previously received an anthracycline, a taxane and capecitabine?
    - **Monotherapy does appear to have activity in advanced breast cancer.**

3) Are the risks of peripheral neuropathy with ixabepilone therapy acceptable for the given benefit?
    - **The incidence of neurotoxicity is unacceptably high in all the ixabepalone trials. QOL is important and must be balanced with the 70% incidence neuropathy.**
    - **Clearly changes in the dose and/or schedule of ixabepilone need to be addressed.**

4) Is the degree of neutropenia seen with ixabepilone therapy acceptable in this patient population?
    - **No. The incidence of grades 3 and 4 myelosuppression exceeded 50%.**

5) What, if any, further monitoring or clinical investigations for cardiac toxicity are necessary.
    - **Pursue phase 4 commitments.**

6) Do you have any suggestions for studies that the sponsor may perform to more accurately define and potentially improve the safety profile of ixabepilone?

    - **I have serious concerns about neuropathy and myelosuppression. Modifications in dose and/or schedule should be addressed to determine if toxicity can be minimized.**

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

/s/

Sharon Thomas
10/15/2007 12:40:34 PM
CSO

Ramzi Dagher
10/16/2007 09:00:14 AM
MEDICAL OFFICER

Thomas, Sharon

From: Thomas, Sharon
Sent: Monday, October 15, 2007 12:19 PM
To: 'heather.knighttrent@bms.com'
Subject: FW: Ixabepilone NDA

Dear Heather,

Please respond as soon as possible to the CMC request below regarding PMC #6. Please don't hesitate to contact me if you have any questions.

Thanks,
Sharon

- **It seems that the response from the firm regarding the post-marketing commitment to address dual packaging is not timely. Please send this comment. "Provide a commitment that by April, 2008, you will submit a proposal to address the issue of banding of the vial and the diluent."**

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: October 10, 2007

TO: Sharon Thomas, Regulatory Project Manager, DDOP, HFD-150
Ramzi Dagher, M.D., Medical Team Leader, OND/OODP/DDOP
Robert Justice, M.D., Medical Officer, OND/OODP/DDOP

THROUGH: Joseph P. Salewski, Acting Branch Chief, Good Clinical Practice Branch II (HFD-47)
Division of Scientific Investigations

FROM: J. Lloyd Johnson, Pharm.D., Good Clinical Practice Branch II (HFD-47)
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: NDA 22-065

APPLICANT: Bristol-Myers Squibb Squibb Company

DRUG: Ixabepilone (BMS-247550)

CHEMICAL CLASSIFICATION: 1S (New Molecular Entity; Priority Review)

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Metastatic or locally advanced breast cancer as monotherapy and in combination with capecitabine

CONSULTATION REQUEST DATE: June 14, 2007

GOAL DATE TO PROVIDE CLINICAL INSPECTION SUMMARY: October 12, 2007

PDUFA DATE: October 16, 2007

I. BACKGROUND

Bristol-Myers Squibb (BMS) submitted an NDA for ixabepilone, the first of a new class of epothilones analog antineoplastic agents for the treatment of metastatic breast cancer (MBC) resistant to, or failed, prior cytotoxic chemotherapy (including anthracycline, taxane, and capecitabine). Epothilones are a new class of non-taxane agents reported to exhibit cytotoxic activities and antitumor activities against a broad range of taxane sensitive and taxane resistant human tumor models. Ixabepilone is a semi-syntnthetic derivative of the natural product epothilone B. The sponsor reports that Phase I and II trials of ixabepilone demonstrate antitumor activity in cancers of the ovary, cervix, colon, stomach, breast melanoma, non-small cell lung carcinoma, and non Hodgkins' lymphoma. The product is also reported to demonstrate activity in patient with both taxane sensitive and resistant breast cancer as well as other tumor types when used in combination with capecitabine or as monotherapy in patients who failed anthracycline and taxane cytotoxic chemotherapy.

The sponsor submitted safety and efficacy data from Pivotal Studies CA 163081 (monotherapy study) and CA 163046 (combination therapy) and several Phase II and Phase III studies in subjects with metastatic or locally advance breast cancer that failed prior chemotherapy including anthracycline, taxane, or capecitabine.

The sponsor claims that based on submitted data from two pivotal combination therapy studies and three pivotal monotherapy studies, ixabepilone in combination with capecitabine or as monotherapy provides significant improvement and durable response in MBC subjects who have exhausted current available treatments.

The primary focus of this inspection will be Study Protocols CA 163081 and CA 163046.

II. RESULTS (by site):

NAME	CITY, STATE	COUNTRY	PROTOCOL	INSPECT DATE	EIR-REC'VD	CLASS.
Nuhad Ibrahim, M.D.	Houston, TX	USA	CA 163046 and CA 163081	Aug. 22 – 27, 2007	Pending	NAI
Rubi Khaw Li, M.D.	Quezon City	Philippines	CA 163046	Sept. 25 – 28, 2007	Pending	NAI
Bristol-Myers Squibb Company	Wallingford, CT	USA	CA 163046 and CA 163081	Sept. 11 – 17, 2007	Pending	NAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr= Deviation(s) form regulations, response requested. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection/Report not completed

Study Protocol:

Protocol CA163046 - A Phase III Trial of Novel Epothilone BMS-247550 Plus Capecitabine Versus Capecitabine Alone in Patients With Advanced Breast Cancer Previously Treated With or Resistant To an Anthracycline and Who are Taxane Resistant

Protocol CA163081 - A Phase 2 Trial of Novel Epothilone BMS-247550 in Patients with Advanced Cancer Who Are Resistant to An Anthracycline, a Taxane, and Capecitabine

Clinical Study CA 163046:

CA163046 is the primary safety and efficacy study for the combination therapy indication conducted in subjects with MBC who failed or were resistant to anthracyclines and taxanes. The study is a randomized Phase 3 study with ixabepilone plus capecitabine vs. capecitabine alone. The primary study objective is to compare efficacy progression free survival (PFS) (time to progression) in subjects with advanced breast cancer previously treated with or resistant to an anthracycline, and who are taxane resistant. The secondary endpoint is to compare overall survival in the same subject population. Eligible subjects included ≥18 Y/O women with mestastatic or locally advanced breast cancer not curable by surgery or radiation (please see protocol for complete inclusion and exclusion criteria).

Study subjects received ixabepilone 40 mg/m^2 IV over 3 hours on Day 1 of a 21-day cycle, plus capecitabine 1000 mg/m^2 twice daily administered orally on Days 1 to 14 of a 21-day cycle for a maximum of 18 cycles until disease progression or unacceptable toxicity.

A total of 746 subjects were treated (369 in the ixabipilone plus capecitabine arm; 377 in the capecitabine arm). An interim analysis was conducted after the first 450 subjects were randomized. The study had an independent Data Monitoring Committee (DMC) that oversaw the safety and efficacy of the study.

Safety assessments included adverse events, serious adverse events, and laboratory abnormalities.

The study was initiated on Sept. 4, 2003 and concluded on Dec. 12, 2006. The study was conducted in 160 study centers covering 22 countries.

Clinical Study CA163081:

CA163081, was the primary safety and efficacy study for the monotherapy indication. The study was a multi-national, multi-center, single-arm study on efficacy and safety of ixabepilone in subjects with metastatic or locally advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine.

An external independent radiology review committee (IRRC) reviewed the tumor scans and assessed tumor response. The investigator also determined tumor response.

128 subjects were enrolled and 126 were treated. Subjects were treated for a maximum of 18 cycles or until evidence of progressive disease (PD) and or the patient met discontinuation criteria.

The primary efficacy endpoint was objective response rate (ORR), defined as the number of patients with a best response of complete response (CR) or partial response (PR), as assessed by the IRRC, divided by the total number of response-evaluable patients.

Secondary efficacy endpoint assessments included duration of response, progression-free survival, and time to response and overall survival.

Safety assessments included adverse events, serious adverse events, and laboratory abnormalities.

The study was initiated on February 24, 2004 and concluded on May 6, 2005. The study was conducted in 36 study centers.

The inspections audited two domestic clinical investigators that participated in the study and a sponsor/monitor inspection. The clinical investigator inspections were conducted under the Bioresearch Monitoring Program (CP 7348.811), the sponsor/monitor inspection was conducted under (CP 7348.810). The clinical investigator and sponsor audits were issued by DSI in consultation with the NDA Review Committee.

Basis for site selection:

The Division of Oncologic Drug Products (DODP) selected two clinical investigator study sites based on evaluation of data submitted in the NDA supplement. The two sites were inspected to validate data submitted in support of the efficacy supplement. In addition, DSI issued a routine sponsor/monitor inspection to be conducted in conjunction with the clinical investigator inspections for this NDA.

(1) Nuhad Ibrahim, M.D. (Study 163046 – 13 Subjects) and (CA 163081 – 22 Subjects)
UT MD Anderson Cancer Center, Dept. of Breast Medical Oncology
Unit 1324 1515
Holcombe Blvd Houston, TX 77030

Inspection dates: August 20 – 27, 2007

Methodology: Inspection assignments were issued to the field office.

a. What was inspected?
A comprehensive audit of the study records of 8 subjects enrolled in the study.

b. Limitations of inspection: None

c. General observations/commentary:

DAL-DO's Investigator Patrick Stone reported that the inspection focused on the investigator's conduct and records pertaining to the two protocols (CA163-081 & CA163-046). The audit included a review of the investigator's regulatory records and correspondence for both studies. Source documents of all 13 subjects for CA163-081 and at least 14 subjects for CA163-046 were compared to CRF's & sponsor's data listings. All subjects signed approved informed consent, and protocols received Institutional Review Board (IRB) approval before enrolling subjects. No objectionable conditions were found.

No FDA Form 483 was issued.

Recommendation: Data from site are acceptable. Preliminary review does not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

(2) Bristol-Myers Squibb Company
5 Research Pkwy
Wallingford, CT 06492

Inspection dates: September 11 – 17, 2007

Methodology: Inspection assignments were issued to the field office.

a. What was inspected? A comprehensive review of the study records of subjects enrolled in Study CA163-081 & CA163-046

b. Limitations of inspection: None

c. General observations/commentary:

The inspection covered sponsor/monitor practices related to protocol CA163-081 & CA163-046. Study records were reviewed to verify documentation that general responsibilities of a sponsor were met.

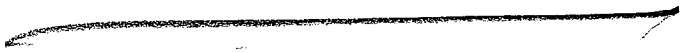
Documentation showing selection of qualified investigators, financial disclosure and training of clinical investigators were reviewed. Procedures for how the sponsor addressed problems encountered with the investigators, selection of qualified monitors, and monitoring reports were reviewed. Tracking procedures for adverse events, serious adverse events, deaths, and discontinuations of subjects were also reviewed. The firm had good documentation to show that FDA and other clinical investigators were informed of significant new adverse effects or risks.

Written agreements for the transfer of obligations were also reviewed. Test article accountability were verified with certificate of analyses for the test article. Computer validation summary reports for EDM and ESF were also reviewed. No discrepancies were noted.

No FDA Form 483 was issued.

Recommendation: Data from site are acceptable. Preliminary review does not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

DSI Complaint Case #1997:



(3) Rubi Khaw Li, M.D. (Study 163046) (21 Subjects)
St. Luke's Medical Center
Room 512 279 East Rodriguez St. Boulevard
Quezon City, 1102 Philippines

Inspection dates: September 25 – 28, 2007
Methodology: Inspection assignments were issued to the field office.

a. What was inspected?
A comprehensive review of the complete study records of 7 subjects and random review of 3 additional subject records out of 21 total subjects entered in the study.

b. Limitations of inspection: None

c. General observations/commentary:

The audit and comparison of sponsor's data listings against source documents, IRB correspondence, consent forms, test article accountability, adverse event reporting, protocol adherence and sponsor monitoring records and documentations were all found to be in good order. The inspection revealed no significant findings or objectionable conditions that would impact approval. At the conclusion of the inspections, several discussion points were discussed with Dr. Li and her staff concerning IRB continuing review procedures, procedures for better accountability of returned drugs and better documentation procedures for proper correction of study records.

No FDA Form 483 was issued.

Recommendation: Data from site are acceptable. Preliminary review does not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Observations noted above are based on preliminary results and communications from the FDA Field Investigators. An inspection summary addendum will be generated if conclusions changes significantly upon receipt and review of the pending EIR.

In general, based on the inspection of two clinical study sites combined with the sponsor/monitor inspection for this NDA, it appears that sufficient documentation to assure that study subjects audited at those two sites did exist, study eligibility criteria were fulfilled, participants received assigned study medications, and adverse events were adequately reported. Primary endpoints and secondary endpoints were captured in accordance with protocol requirements. Therefore, based on the results of the study sites inspected, data submitted in support of this application are

acceptable and determined to be valid and reliable.

Follow-up action: An inspection summary addendum will be generated if conclusions changes significantly upon receipt of and review of all pending EIRs or if any significant information regarding the complaint case is received by DSI.

{See appended electronic signature page}

J. Lloyd Johnson, Pharm.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments:

{See appended electronic signature page}

Joseph P. Salewski
Acting Branch Chief, Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

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/s/

J. Lloyd Johnson
10/11/2007 11:38:20 AM
PHARMACOLOGIST

Joseph Salewski
10/11/2007 01:52:02 PM
CSO

3 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative-_____

Bristol-Myers Squibb Company

5 Research Parkway Wallingford, CT 06492-7660 203-677-6000

AMENDMENT:
Response to Post Marketing Study Commitments

NDA # 22-065
Ixabepilone (BMS-247550)
Sequence #0023

October 10, 2007

Robert Justice, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Justice:

Reference is made to NDA 22-065 submitted on April 16, 2007 and to the FDA email on October 9, 2007 from Ms. Sharon Thomas containing Post Marketing Study Commitments.

The purpose of this submission is for Bristol-Myers Squibb (BMS) to respond to the aforementioned request.

If there are any questions or comments concerning this submission, please contact the undersigned at (203) 677-3858 or heather.knighttrent@bms.com.

Sincerely,

A. Heather Knight-Trent

A. Heather Knight-Trent, Pharm.D.
Director
Global Regulatory Science
Bristol-Myers Squibb Company

COMMITMENT 1

Description of Commitment: To submit the complete study report and datasets for the ongoing clinical study CA163048 entitled "A Phase 3 Trial of Novel Epothilone BMS-247550 plus Capecitabine versus Capecitabine Alone in Patients with Advanced Breast Cancer Patients Previously Treated with An Anthracycline and a Taxane"with a primary endpoint of overall survival following the collection of data for a prespecified number of events (deaths), or earlier if recommended by the independent data monitoring committee.

Final Report Submission:

RESPONSE

BMS commits to submit the final report in December 2008.

COMMITMENT 2

Description of Commitment: To submit the final study report and datasets for the study CA163046 "A Phase III Trial of Novel Epothilone BMS-247550 Plus Capecitabine Versus Capecitabine Alone in Patients With Advanced Breast Cancer Previously Treated With or Resistant To an Anthracycline and Who are Taxane Resistant" after collection of overall survival data following the prespecified number of deaths for a mature analysis.

Final Report Submission and Datasets:

RESPONSE

BMS commits to submit the final report in October 2008.

COMMITMENT 3

Description of Commitment: Submit the completed report for the rifampin drug-drug interaction evaluation and datasets for study CA163102.

Final Submission Report: September 2009

RESPONSE

BMS commits to submit the final report in September 2009.

COMMITMENT 4

Description of Commitment: An in-vitro assessment to determine if ixabepilone is a P-glycoprotein substrate or inhibitor needs to be conducted.

Final Submission Report: September 2009

RESPONSE

BMS commits to submit the final report in September 2009.

COMMITMENT 5

Description of Commitment: To design, conduct and submit the completed study report and datasets for a study to assess the potential for ixabepilone to prolong the QT interval in patients.

Protocol Submission: May 2008
Study Start: September 2008
Final Report Submission: September 2009

RESPONSE

BMS commits to submit the following:

Protocol Submission: May 2008
Study Start: September 2008
Final Report Submission: December 2010

COMMITMENT 6

It seems that the response from the firm regarding the post-marketing commitment to address dual packaging is not timely. Please send this comment. "Provide a commitment that by April, 2008, you will submit a proposal to address the issue of banding of the vial and the diluent."

RESPONSE

BMS commits to provide the following for PMC #6:

Description of Commitment: Submit a packaging amendment to physically link the drug vial and diluent vial.

Proposal Submission: April 2008
Packaging Amendment Submission: April 2009

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	October 5, 2007
To:	Robert Justice, M.D., Director Division of Drug Oncology Products
Thru:	Toni Piazza-Hepp, Pharm.D., Deputy Director Division of Surveillance, Research and Communication Support
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist Division of Surveillance, Research and Communciation Support
Subject:	DSRCS review of Patient Labeling (Patient Package Insert)
Drug Name(s):	TRADENAME Kit (ixabepilone) for Injection, for intravenous infusion only
Application Type/Number:	22-065
Applicant/sponsor:	Bristol-Myers Squibb Company
OSE RCM #:	2007-1285

1 INTRODUCTION

Bristol-Myers Squibb Company submitted a New Drug Application, NDA# 22-065 for TRADNAME (ixabepilone) for injection on April 16, 2007. The application proposes the following indications:

- "TRADENAME is indicated in combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline and a taxane."
- "TRADENAME is indicated as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to cytotoxic chemotherapy. Previous therapy should have included an anthracycline, a taxane, and capecitabine."

The Review Division further revised the draft Professional Information on September 21, and September 28, 2007.
The Division of Surveillance, Research and Communication Support has been requested by the Review Division to review Patient Labeling (in the form of a Patient Package Insert or PPI), submitted with this NDA.

2 MATERIAL REVIEWED

Revised draft Professional Information and PPI dated September 21 and September 28, 2007.

3 DISCUSSION

See the attached document for our recommended changes to the proposed PPI (marked up and clean). Comments to the review division are ***bolded, underlined and italicized.***
We have simplified the wording where possible, made it consistent with the Professional Information (PI), moved some of the information to different sections, and removed unnecessary information. Although not required for Patient Information, we have also put this PPI in the question-answer format specified in the Medication Guide Regulations (21 CFR 208.20) that we are recommending for all FDA-approved patient labeling. These recommendations are consistent with current research to improve risk communication to a broad range of audiences including those with lower literacy levels.
All future relevant changes to the PI should also be reflected in the PPI.

4 CONCLUSIONS AND RECOMMENDATIONS

- A PPI for TRADENAME is voluntary. However, TRADENAME is for intravenous infusion only. Patients will not present a prescription at a pharmacy, which is where they are most likely to receive a PPI. The sponsor should clarify how they intend to distribute the PPI to patients.
- The proposed PPI as submitted by the sponsor has a Flesch-Kincaid Grade Level of 9.8 and a Flesch Reading Ease score of 49.1. To enhance comprehension, patient materials should be written at a 6th to 8th grade reading level , and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). We have improved the readability scores. Our revised PPI has a Flesch Kincaid grade level of 7.9 and a Flesch Reading Ease score of 58.3.
- We have added the following sections to the PPI:
    - "What is the most important information I should know about TRADENAME?" This section was added to convey the important information from the black box warning in the PI using patient-friendly language.
    - "What should I tell my healthcare provider before receiving TRADENAME?" This section conveys important information about drug interactions and other information that both patient and healthcare provider should be aware of.
- In the section, "What are the possible side effects of TRADENAME," we have ordered the serious side effects to reflect the boxed warning first, and then according to the order in which they appear

in Section 5 *Warnings and Precautions*, in the PI. We recommend revising the order as appropriate.

- We have added additional information about hand-foot syndrome so that this is not minimized.
- We are providing to the review division a marked-up and clean copy of the PPI. We recommend using the clean copy as the working document.

11 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Administrative-*_____

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/s/

Sharon Mills
10/5/2007 11:33:52 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
10/5/2007 11:40:39 AM
DRUG SAFETY OFFICE REVIEWER

INTERNAL MEETING MINUTES

MEETING DATE: October 5, 2007 **TIME:** 1:30 pm EST

LOCATION: FDA White Oak Facility, Conference Room 2201

NDA: 22-065

DRUG: Ixabepilone

INDICATION: As monotherapy and in combination with capecitabine in advanced, metastatic breast cancer

SPONSOR: Bristol-Myers Squibb Company

TYPE OF MEETING: Pre-approval Safety Conference

PARTICIPANTS:

DDOP:
Richard Pazdur, Robert Justice, Ramzi Dagher, Edvardas Kaminskas, Robert Lechleider, Robeena Aziz, Xiaoping Jiang,
OSE:
Sam Chan, Bob Pratt, Sharon Mills, [redacted] Linda Kim-Jung,

AGENDA:
DDOP presented review findings and recommendations for Warnings and Precautions in labeling for review and discussion:

Peripheral Neuropathy:
Peripheral neuropathy occurred in 70% of patients treated with ixabepilone. In the randomized trial, 23% of patients in the combination arm had grade 3 or 4 neuropathy compared to none in the capecitabine alone arm. In the monotherapy trial, grade 3 / 4 peripheral neuropathy occurred in 14% of patients.

Myelosuppression:
Significant myelosuppression occurred. More than half the patients experienced grade 3 or 4 thrombocytopenia.

Hepatic impairment:
An unacceptable risk of death was found in patients with moderate or severe hepatic impairment treated with ixabepilone in combination with capecitabine. Five of sixteen patients with moderate or severe hepatic insufficiency treated with the combination died, compared with 7 of 353 patients with normal hepatic function or mild insufficiency.

Ixabepilone should not be used in combination with capecitabine in the presence of moderate or severe hepatic insufficiency. The agreed upon labeling includes a box warning contraindicating the use of ixabepilone in combination with capecitabine in patients moderate or severe hepatic insufficiency defined by AST / ALT / bilirubin.

ACTION ITEMS:

- It was recommended that OSE monitor the above AEs post approval:

Ramzi Dagher, M.D. chaired the meeting. Sharon Thomas facilitated the meeting.

Prepared by:

Sharon Thomas
Regulatory Project Manager, DDOP

Sam Chan
Regulatory Project Manager, OSE

Bristol-Myers Squibb Company

5 Research Parkway Wallingford, CT 06492-7660 203-677-6000

AMENDMENT:
Response to Post Marketing Study Commitments

NDA # 22-065
Ixabepilone (BMS-247550)
Sequence #0021

October 4, 2007

Robert Justice, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Justice:

Reference is made to NDA 22-065 submitted on April 16, 2007 and to the FDA email on October 2, 2007 from Ms. Sharon Thomas containing Post Marketing Study Commitments.

The purpose of this submission is for Bristol-Myers Squibb (BMS) to respond to the aforementioned request.

If there are any questions or comments concerning this submission, please contact the undersigned at (203) 677-3858 or heather.knighttrent@bms.com.

Sincerely,

A. Heather Knight-Trent

A. Heather Knight-Trent, Pharm.D.
Director
Global Regulatory Science
Bristol-Myers Squibb Company

Thomas, Sharon

From: Thomas, Sharon
Sent: Tuesday, October 02, 2007 9:32 AM
To: 'heather.knighttrent@bms.com'
Subject: FW: Statistical request to the sponsor of NDA22065/Ixbepilone

Dear Heather,

Please respond to the following urgent statistical requests as soon as possible. Please don't hesitate to contact me if you have questions.

Thanks,
Sharon

1. **Please provide clarification about the following confused information regarding the date that was used to calculate the duration of the response for patient ID CA163081-4-97 in study CA163081.**

- **In Table 1 of your response to FDA clinical review team query dated 25-June-2007, the date of death ( ) was used as the progression date to calculate the duration of response; the duration of response was 12.3 months.**
- **In Table 10.1.1.1A of the clinical study report, duration of PR for this patient was 1.7 months, censored on the date of her last tumor assessment (as determined by IRRC data).**
- **In the dataset EFF_RAD for study CA163081, the date that was used to calculate the duration of response for this patient was the last assessment date (08JUN2005).**

2. **Per your response to FDA clinical review team query dated 25-June-2007, the number of responders has been updated from 14 to 15. Please provide the data of this extra responder that needed to conduct the analysis of duration of response for the updated 15 responders.**

Thomas, Sharon

From: Thomas, Sharon
Sent: Monday, September 24, 2007 2:39 PM
To: 'heather.knighttrent@bms.com'
Subject: RE: Ixabepilone NDA 22065
Importance: High

Dear Heather,

The clinical reviewers are looking for adverse events, grade 3 or 4, and SAEs in patients more than 65 years of age and 65 and younger, and any other population subsets, such as race and hepatic impairment in study CA163081. If they were performed, where can we find them?

Thanks,
Sharon

Thomas, Sharon

From: Thomas, Sharon
Sent: Friday, September 21, 2007 8:48 PM
To: 'heather.knighttrent@bms.com'
Subject: Urgent: Statistical request for -NDA 22065, ixabepilone

Importance: High

Dear Heather,

The statistical team cannot finalize the label until they receive the results of the PFS analysis requested on 9/13/07. **Please let me know as soon as possible when you can provide this information.**

Thanks,

Sharon

Appears This Way
On Original

Thomas, Sharon

From: Thomas, Sharon
Sent: Wednesday, September 19, 2007 10:40 AM
To: 'heather.knighttrent@bms.com'
Subject: Re: NDA 22-065, ixabepilone

Heather,

Please refer to your NDA 22-065, submitted for the use of ixabepilone. Please respond to the following CMC request as soon as possible.

"Provide [redacted] for the 15 mg and 45 mg vials and the vehicle for constitution vials. Also confirm that these settings are supported by the container closure integrity test results".

Please don't hesitate to contact me if you should have any questions.

Thanks,
Sharon

Appears This Way
On Original

Thomas, Sharon

From: Thomas, Sharon
Sent: Tuesday, September 18, 2007 10:19 AM
To: 'heather.knighttrent@bms.com'
Subject: RE: CMC request for Ixabepilone NDA 22065

Dear Heather,

Please find below additional CMC comments for ixabepilone. Please respond as soon as possible.

Thanks,
Sharon

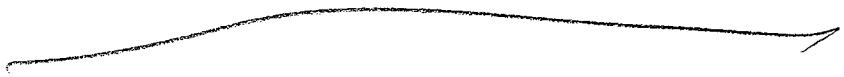
1. Provide test methods that are used in addition to the NF methods for purified polyoxyethylated castor oil.

2. To prepare a 0.2 mg/mL solution, each mL of the constituted IXEMPRA containing 2 mg/mL ixabepilone will need to be diluted to a total volume of 10 ml with Lactated Ringer's Injection, USP. Provide solubility of ixabepilone (at room temperature) in —(v/v) POE castor oil — (v/v) ethanol — Lactated Ringer's Injection, USP.

3. We have following additional comments concerning the revised carton and the vial labels submitted to us. Provide accordingly revised draft labels.

a. In the label for paper board folding carton :

- To reduce clutter, we recommend that the wording "Dosage and Administration" on the side panel should be deleted as it does not seem to add value to product label.
- The storage statements on the side panel should be bolded and a space be left between the storage statements and the warning statement.
- Submit mock up of actual size carton labels for both strengths.



c. In the label for vehicle for constitution:

- Submit mock up of actual size vial labels for both strengths.

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/s/

Sharon Thomas
9/19/2007 05:12:06 PM
CSO

Thomas, Sharon

From: Thomas, Sharon
Sent: Monday, September 17, 2007 3:43 PM
To: 'heather.knighttrent@bms.com'
Subject: FW: Ixabepilone NDA 22065
Attachments: emfinfo.txt

We are aware of this. It's being handled appropriately.

Thanks,
Sharon

From: heather.knighttrent@bms.com [mailto:heather.knighttrent@bms.com]
Sent: Monday, September 17, 2007 9:07 AM
To: Thomas, Sharon
Subject: Ixabepilone NDA 22065

Dear Sharon,

Thank you for the follow-up last Monday, September 10. Do you have any status update information regarding the tradename, timing of labeling revisions? The manufacturing site in Ireland was informed of an inspection on October 15-18, 2007. This is also completing after the action date. Will this have any impact on the action date? The inspector told the Baxter manufacturing site that they did not have the CMC section of the dossier. I have not received any requests, so is the review division providing this information as needed to them?

Thanks,
Heather

Thomas, Sharon wrote:

> Heather,
>
> We would prefer w/v amounts in all labels. Also, I'm still waiting on a response from DMETS and DSI regarding the ixabep. tradename and inspections. I will ask the team at the next labeling mtg. when I can provide you with our changes to the label.
>
> Thanks,
> Sharon
>
> ---
>
> **From:** heather.knighttrent@bms.com [mailto:heather.knighttrent@bms.com]
> **Sent:** Monday, September 10, 2007 12:01 PM
> **To:** Thomas, Sharon
> **Subject:** Re: CMC request for Ixabepilone NDA 22065
>
> Dear Sharon,
>
> The team requires further clarification on the following:

1 Page(s) Withheld

____ Trade Secret / Confidential

1 Draft Labeling

____ Deliberative Process

Withheld Track Number: Administrative-_____

From: Thomas, Sharon
Sent: Thursday, September 13, 2007 3:03 PM
To: 'heather.knighttrent@bms.com'
Subject: NDA 22-065, ixabepilone statistical request

Dear Heather,

Please respond to the statistical request below as soon as possible.

Thanks,
Sharon

1. **Please confirm that in the submitted result of the primary analysis of PFS, the PFS was censored at the date of last assessment date prior to the earliest start date of any subsequent therapy for the patients who received subsequent therapy regardless of having progression.**

2. **If the answer to 1) is no, please perform the PFS analysis by using the censoring scheme as mentioned in 1) for the patients who received subsequent therapy regardless of having progression.**

3. **Please provide dataset(s) and SAS programs with description that produce the result of PFS analysis mentioned in 2).**

4. **Please provide the names of datasets and variables (including location of variables) that produce the result of PFS analysis mentioned in 2).**

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/s/

Sharon Thomas
9/13/2007 04:00:54 PM
CSO

From: Thomas, Sharon
Sent: Tuesday, September 11, 2007 4:20 PM
To: 'heather.knighttrent@bms.com'
Subject: NDA: 22-065, ixabepilone

Dear Heather,

Please respond as soon as possible to the clinical comment below.

Thanks,
Sharon

Dataset AESAE.xpt does not appear to contain a heading for treatment. In order to generate a table such as Table 2.1.1C in the Summary of Clinical Safety such information is needed. Please provide a breakdown of planned treatment administered for studies 031 and 046. For 031 this would be the different dosing schedules and for 046 it would be capecitabine versus ixabepilone plus capecitabine. If this information (mapping AEs to treatment administered) is available in another previously submitted dataset, please indicate where.

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/s/

Sharon Thomas
9/12/2007 11:39:03 AM
CSO

Thomas, Sharon

From: Thomas, Sharon
Sent: Wednesday, September 05, 2007 2:52 PM
To: 'heather.knighttrent@bms.com'
Cc: 'Li-Chun Wang'
Subject: RE: BMS Ixabepilone NDA CMC Update

Heather,

Please find below additional comments from the CMC reviewer. Please respond as soon as possible.

Thanks,
Sharon

1. **The relaxation of the acceptance criteria for heavy metals from [redacted] as proposed in the amendment dated 30-Aug-2007, is not acceptable. If the method is not able to quantify heavy metals separately, the acceptance criteria for heavy metals and the method [redacted] proposed in the original submission should be used.**

2. **Provide the calculations (5 year projections) of the estimated concentration (EIC) of the drug substance at the point of entry into the aquatic environment.**

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/s/

Sharon Thomas
9/7/2007 10:18:14 AM
CSO

Thomas, Sharon

From: Thomas, Sharon
Sent: Tuesday, September 04, 2007 2:52 PM
To: 'heather.knighttrent@bms.com'
Subject: NDA 22-065, ixabepilone

Heather,

How many patients were enrolled at the time of each protocol amendment for protocol CA163046?

Thanks,
Sharon

Thomas, Sharon

From: Thomas, Sharon
Sent: Monday, August 13, 2007 4:16 PM
To: 'heather.knighttrent@bms.com'
Subject: RE: FW: NDA 22-065, Ixabepilone for injection

Dear Heather,

Please find the answers to your questions submitted earlier today.

Thanks,
Sharon

1. What is the current status of the Tradename review? Your voicemail following the 90 day review meeting indicated that it was expected to be completed on August 10, 2007. Yes, but unfortunately it's still under review.
2. What is the status of pre-approval inspection (PAI)? Ongoing. Will inspections occur? Yes.
3.

From: heather.knighttrent@bms.com [mailto:heather.knighttrent@bms.com]
Sent: Monday, August 13, 2007 9:01 AM
To: Thomas, Sharon
Subject: Re: FW: NDA 22-065, Ixabepilone for injection

Dear Sharon,

Thank you for sending these questions. The team is currently working on the responses and will provide answers as soon as possible. I also have the following questions regarding the NDA review and IND for ixabepilone.

1. What is the current status of the Tradename review? Your voicemail following the 90 day review meeting indicated that it was expected to be completed on August 10, 2007.
2. What is the status of pre-approval inspection (PAI)? Will inspections occur?
3.

Sincerely,
Heather

Thomas, Sharon wrote:

> Dear Heather,
>
> Please find attached the CMC request for ixabepilone. Please respond as soon as possible.

Please let me know if you have any questions.

Thanks,
Sharon

Thomas, Sharon

From: Thomas, Sharon
Sent: Thursday, July 12, 2007 4:07 PM
To: 'heather.knighttrent@bms.com'
Subject: RE: NDA 22-065; ixabepilone

Dear Heather,

We have the following request/comments from the Statistical Review Team. Please refer following requests to study CA163046.

1. **Please provide the dataset (one record per patient) that contains the following 3 stratification factors that were used in the primary analysis of PFS as soon as possible.**
   - **Presence of visceral metastases in liver and/or lung: (1="yes", 2="no");**
   - **Minimum of either doxorubicin 240 mg/m2 or epirubicin 360 mg/m2 and relapse > 6 months in adjuvant setting: (1="yes", 2="no");**
   - **Prior chemotherapy for metastatic disease (1="yes", 2="no").**

   If the dataset was provided when the NDA was submitted, please provide the name of the variables for the 3 stratification factors and the name of the dataset as soon as possible.

2. **Please provide the number of PFS events when the planned interim analysis of PFS was performed on the first 450 randomized patients.**

Please don't hesitate to contact me should you have any questions.

Regards,
Sharon

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/s/

Sharon Thomas
7/14/2007 12:19:24 PM
CSO

Thomas, Sharon

From: Thomas, Sharon
Sent: Thursday, June 28, 2007 4:17 PM
To: 'heather.knighttrent@bms.com'
Cc: 'krisztina.nemenyi@bms.com'
Subject: NDA 22-065/ixabepilone

Dear Heather,

The clinical team would like to have the following information regarding CA163081 in order to complete the review.

1. **You have submitted, on April 17, 2007, data as of December 21, 2005. These are old data.**

2. **Please submit an updated Efficacy Section, including updated Tables 8.1, 9.1A, 9.1B, 10A, 10B, 10C, 10.1.1.1A, 10.1.1.1B, 10.1.1.1C, 10.1.1.1D, 10.1.1.2, 10.1.2A, 10.1.B, 10.1.3, Figures 10.2A, B, C, and D. If there are no changes, please so state.**

3. **Please submit an update Safety Section, including updated Tables 12, 12.1.1, 12.2, 12.3, 12.4, 12.5.1A and B, 12.5.2, 12.5.2.1, 12.5.2.2, and Figures 12.5.2.4A and B. If there are no changes, please so state.**

Let me know if you have any questions.

Thank you,
Sharon

****

Sharon P. Thomas, BS, RHIT, CCRP
Consumer Safety Officer
Division of Drug Oncology Products
Center for Drug Evaluation and Research, FDA
Phone: (301) 796-1994
Fax: (301) 796-9849
Email: Sharon.Thomas@fda.hhs.gov

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/s/

Sharon Thomas
6/28/2007 04:21:07 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-065

Bristol-Myers Squibb Company
5 Research Parkway
Signature 91, 3Sig-509
Wallingford, CT 06492

Attention: Heather Knight-Trent, PharmD
Director, Global Regulatory Sciences

Dear Ms. Knight-Trent:

Please refer to your April 16, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ixabepilone (BMS-247550) Injection, Powder, Lyophilized for Solution, for intravenous use received April 16, 2007.

In our filing review, we have identified the following potential review issues:

1. The drug name must be followed by the drug's dosage form and *route of administration* (e.g. Note that "For Injection" is a dosage form not a route of administration (i.e., intravenous). [See 21 CFR 201.57(a)(2)]

2. Please add one line of white space above the heading for Dosage and Administration.

3. Do not refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format, "available at http://www.fda.gov/cder/guidance.

4. Avoid using "trailing" zeros after whole numbers (e.g., see 2.4 Instructions for IV Administration). Please refer to the Institute for Safe Medication Practices website at http://www.ismp.org/Tools/abbreviationslist.pdf for a list of error-prone abbreviations, symbols, and dose designations.

5. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]

6. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c) (18)] The reference [See FDA-Approved Patient Labeling] should appear at the beginning of the Patient Counseling Information section to give it more prominence. The new rule [21 CFR 201.57(a)(4) requires that the verbatim statement, *"See full prescribing information for complete boxed warning"* must be placed immediately following the heading of the Boxed Warning.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions please call me at (301) 796-1994.

Sincerely,
{See appended electronic signature page}
Sharon Thomas, BS, RHIT, CCRP
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Sharon Thomas
6/27/2007 06:37:56 PM

Thomas, Sharon

From: Thomas, Sharon
Sent: Monday, June 25, 2007 9:30 AM
To: 'heather.knighttrent@bms.com'
Cc: 'krisztina.nemenyi@bms.com'
Subject: NDA 22-065; ixabepilone

Dear Heather,

We have the following request/comments from the Clinical Review Team.

Please provide an update on patients with partial responses in study CA163081. Specifically, we are looking for duration of response, PFS and survival on the 6 patients still in response at the time of datalock.

Please don't hesitate to contact me should you have any questions.

Regards,
-sharon

****

Sharon P. Thomas, BS, RHIT, CCRP
Consumer Safety Officer
Division of Drug Oncology Products
Center for Drug Evaluation and Research, FDA
Phone: (301) 796-1994
Fax: (301) 796-9849
Email: Sharon.Thomas@fda.hhs.gov

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/s/

Sharon Thomas
6/25/2007 04:55:42 PM
CSO

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Drug Oncology Products

Application Number: N22-065

Name of Drug: Ixabepilone (BMS-247550) Intravenous

Applicant: Bristol-Myers Squibb Company

Material Reviewed:

Submission Date(s): April 16, 2007

Receipt Date(s): April 16, 2007

Submission Date of Structure Product Labeling (SPL): April 16, 2007

Type of Labeling Reviewed: WORD

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in your proposed labeling.

Highlights:

- The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]

Full Prescribing Information (FPI):

- Do not refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format, "available at hhtp://www.fda.gov/cder/guidance.
- Avoid using "trailing" zeros after whole numbers (e.g., see 2.4 Instructions for IV Administration). Please refer to the Institute for Safe Medication Practices website at

http://www.ismp.org/Tools/abbreviationslist.pdf for a list of error-prone abbreviations, symbols, and dose designations.

- The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA-Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.

Recommendations

Please address the identified deficiencies/issues and re-submit labeling. This updated version of labeling will be used for further labeling discussions.

_____

Sharon Thomas, B.S., RHIT, CCRP
Regulatory Project Manager

Supervisory Comment/Concurrence:

_____

Dottie Pease
Chief, Project Management Staff

Drafted: st/June 15, 2007
Revised/Initialed:
Finalized:
Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW OF PLR FORMAT

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/s/

Sharon Thomas
6/15/2007 04:07:22 PM
CSO

Dotti Pease
6/18/2007 09:06:34 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-065

NDA ACKNOWLEDGMENT

Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492

Attention: Heather Knight-Trent, PharmD
Director, Global Regulatory Sciences

Dear Ms. Knight-Trent:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Ixabepilone (BMS-247550) Intravenous, 15 mg/vial and 45 mg/vial

Review Priority Classification: Priority

Date of Application: April 16, 2007

Date of Receipt: April 16, 2007

Our Reference Number: NDA 22-065

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 15, 2007, in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be October 16, 2007.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call me at (301) 796-1994.

Sincerely,

{See appended electronic signature page}

Sharon Thomas, B.S., RHIT, CCRP
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Sharon Thomas
6/12/2007 05:43:15 PM

TELECON MINUTES

TELECON DATE: February 15, 2007 **TIME:** 1:00 pm EST

LOCATION: Conf. Room 2205 **APPLICATION:** 58,546

DRUG NAME: ixabepilone (BMS-247550) **TYPE OF MEETING:** Pre-NDA

SPONSOR: Bristol Myers Squibb

Meeting Request Submission Received Date: November 28, 2006
Briefing Document Submission Date: January 11, 2007

FDA ATTENDEES:

Robert Justice, M.D., Division Director, OODP/DDOP
Ann Farrell, M.D., Acting Deputy Director, OODP/DDOP (Chair)
Ramzi Dagher, M.D., Clinical Team Leader, OODP/DDOP
Edvardas Kaminskas, M.D., Clinical Reviewer, OODP/DDOP
Rajeshwari Sridhara, Ph.D., Biostatistics Team Leader, OB/DBV
Brian Bullock, Ph.D., Acting Clinical Pharmacology Team Leader, OCP/DCP5
Julie Bullock, Pharm.D., Clinical Pharmacologist, OCP/DCP5
Frank Cross, Project Manager, OODP/DDOP
Victor Santana, M.D., Visitor

SPONSOR ATTENDEES:

Donna Morgan Murray, PhD, V.P., Global Regulatory Sciences-Oncology and Neuroscience
Heather Knight-Trent, PharmD, Director, Global Regulatory Sciences-Oncology
Renzo Canetta, MD, Vice President, Global Clinical Research-Oncology
David Lee, MD, Vice President, Ixabepilone Global Development
Ronald Peck, MD, Group Director, Global Clinical Research-Oncology
Antonella Maniero, PhD, Director, Biostatistics and Programming
Thomas Kelleher, PhD, Associate Director, Biostatistics and Programming
Marvin Cohen, PhD, Associate Director, Clinical Discovery

BACKGROUND:

On November 28, 2006, the sponsor submitted a request for a pre-NDA meeting to discuss the safety and efficacy results of studies CA163046 and CA163081 and to discuss their NDA submission plan. The background package was submitted on January 11, 2007. The Division held an internal meeting on February 8, 2007, and faxed draft responses to the sponsor on February 9, 2007. The sponsor decided to proceed with the teleconference to obtain clarification. The discussion is documented below in italics.

QUESTIONS for DISCUSSION with FDA RESPONSE AND DECISIONS REACHED:

1. Is the proposed data package sufficient to support filing an NDA for full approval of ixabepilone for the following indications:

FDA Response: Possibly. The Agency made a recommendation that you conduct a planned interim overall survival analysis at the time of final PFS analysis of CA163046 trial (meeting minutes of 3/26/2003, FDA comment to SPA dated 10/22/2004, reiterated in review of SN-256 filed 5/25/06). Have you performed such an analysis? If so, what are the results? Do you have preliminary overall survival or PFS results of the CA163048 trial?

Superiority in PFS in only one trial (CA163046 or CA163048) and not in the other would pose a review issue (minutes of 3/26/2003 meeting).

Discussion: The sponsor stated that no analyses for overall survival have been conducted for Study CA163046 or Study CA163048. For Study CA163046 as of February 15, 2007, there have been 506 deaths (483 deaths at the time of the cutoff of the PFS analysis) out of a planned 631 events. For Study CA 163048, 559 deaths have occurred out of a planned 846 events.

FDA requests that the sponsor submit an interim analysis of OS for Study CA163046 with the planned NDA. This interim analysis would have a boundary for statistical significance of 0.0001. The sponsor expects that the final OS results will be ready by February 2008.

The sponsor is not planning to submit results of Study CA163048 with the proposed NDA.

FDA stated that the sponsor can submit the NDA for regular or accelerated approval but the decision is a review issue.

Data supporting the monotherapy indication (Study CA163081) will be submitted in the NDA simultaneously with the results of combination therapy in Study CA163046.

FDA Response: This will be a review issue. Given the results provided in the meeting package, we strongly discourage the submission of only the monotherapy data.

2. Are the proposed analyses specified in the statistical analysis plan (SAP) for the clinical summary of safety (CSS) acceptable to the FDA? Does the FDA have any comments on the SAP?

FDA Response: Yes, the clinical summary of safety is acceptable.

a. **It appears you have changed your primary endpoint from TTP to PFS for study CA163046. Please explain and provide TTP results (based on investigator assessment and IRRC assessment) as exploratory or supportive.**

Discussion: The sponsor stated that there has been no change in the criteria for the primary efficacy endpoint. This endpoint includes both progression and death from any cause. The sponsor is not doing a separate analysis for TTP.

b. **Please provide OS analysis results based on the data at the final PFS analysis for study CA163046.**

c. **Please provide a derived dataset with one patient per record for efficacy that includes the endpoints PFS (based on investigator assessment and IRRC assessment), TTP, overall survival, PFS as defined for different sensitivity analyses, time to response and duration of response.**

3. The NDA will be submitted in eCTD format as specified in Appendix 4 (Proposal for electronic submission) and Appendix 5 (Draft Table of Contents). Is the proposed format and content of the NDA acceptable to the FDA?

FDA Response: The proposed format is acceptable, but see #1 regarding content.

4. For the Safety Update, BMS proposes to provide a cumulative summary of deaths, serious adverse events, and discontinuations due to adverse events, with a data cutoff of April 2007 for ongoing BMS-sponsored studies, including additional events since database lock for studies CA163046 and CA163081. Per regulations, the Safety Update will be submitted 120 days after submission of the NDA. Is the proposal for the submission of updated safety data acceptable to the FDA?

FDA Response: Please also include a summary of Grades 3 and 4 (NCI CTC) adverse events.

Discussion: The sponsor will provide the above requested information for the pivotal studies only (studies CA 163046 and CA 163081).

ADDITIONAL COMMENTS:

Clinical Pharmacology

1. **Regarding the datasets for the population PK analysis, please submit the following:**

   - **All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.**

   - **Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files can be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt) or as *.pdf files.**

   - **A model development decision tree and/or table which gives an overview of modeling steps.**

   - **The following covariates should be included, at a minimum, in the data set: age, sex, gender, race, grade 3/4 adverse events, and response.**

   Discussion: The sponsor will not be including grade 3/4 adverse events in the PM data set. Instead, a separate adverse event file will be submitted. This adverse event file only contains AEs from the 10 Phase 2 studies. We requested the sponsor to include the 2 phase 1 studies in the AE dataset as well since these studies are part of the PM analysis. The sponsor will attempt to include AE data for the Phase 1 studies.

2. **For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.**

Discussion: *The sponsor said that plots and clinical descriptions will be provided in the NDA. FDA agreed.*

OTHER FDA COMMENTS:

A. REGULATORY

1. NDA/sNDA Presentations to CDER's Division of Oncology

The Center for Drug Evaluation and Research's Division of Drug Oncology Products implemented an initiative in which we request an NDA/sNDA applicant to present their NDA/sNDA to Division personnel shortly after NDA/sNDA submission and before the expected NDA/sNDA filing date. This initiative allows the applicant to present an overview of the entire NDA/sNDA to the review team and interested Division personnel.

These presentations are generally expected to last one hour followed by a half-hour question and answer session. The applicant, not consultants, should present important information on each technical aspect (i.e., clinical, statistical, CMC, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the NDA/sNDA. In addition to providing an overview of the NDA/sNDA, the applicant should present their reasons for why the Division or the Office of Drug Evaluation I should approve their NDA/sNDA.

Please contact your Project Manager shortly after NDA/sNDA submission to schedule a date for your presentation. Alternatively, you may provide available dates in the cover letter of your NDA/sNDA and we will try to accommodate them.

Discussion: *The sponsor agreed.*

2. **Financial Disclosure Final Rule**

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 "*Guidance for Industry: Financial Disclosure By Clinical Investigators*" (posted on the Internet 3/27/2001) at http://www.fda.gov/oc/guidance/financialdis.html.

Discussion: The sponsor will include the requested information in the NDA.

3. **PEDIATRIC RESEARCH EQUITY ACT (PREA)**

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

Discussion: The sponsor will request a Pediatric Waiver with the NDA submission.

4. **PEDIATRIC EXCLUSIVITY**

Pediatric studies conducted under the terms of section 505A of the Federal Food, clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

5. DEMOGRAPHICS

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

CATEGORY		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG
Gender	Males		All Females		Females >50	
Age	0-1 Mo.		1 Mo-2Year		2-12	
	12-16		17-64		65	
Race	White		Black		Asian	
	Other					

Discussion: ***The sponsor inquired whether a cutoff > age 50 rather than > age 65 is a requirement. FDA replied that additional analyses based on this cutoff are required by the Office of Women's Health.***

QT Evaluation

In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Please plan to address this issue early in development.

Discussion: ***The sponsor referred to the April 15, 2005,*** [redacted] ***as indicating no need for clinical studies to assess QT/QTc interval prolongation because of negative in vitro data and data in dogs. FDA stated that our***

position on this issue has been evolving over the last several years. This will not be a filing issue but may be addressed in a Post Marketing Commitment.

Office of Surveillance and Epidemiology (OSE)

- If the sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then the Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).

- For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:

  Premarketing Risk Assessment: http://www.fda.gov/cder/guidance/6357fnl.htm

  Development and Use of Risk Minimization Action Plans: http://www.fda.gov/cder/guidance/6358fnl.htm>

  Good Pharmacovigilance Practices and Pharmacoepidemiologic Assesment: http://www.fda.gov/cder/guidance/6359OCC.htm

  ***Discussion**: The sponsor stated that no Risk Management Plan is planned for the NDA.*

- If there is any information on product medication errors from the premarketing clinical experience, OSE requests that this information be submitted with the NDA/BLA application.

  The sponsor stated there was one case of a reported overdose which will be submitted in the proposed NDA.

- The sponsor is encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.

  ***Discussion**: The sponsor referred to their March 25, 2005, submission of their proposed Tradename. FDA stated that the Tradename will need to be reviewed with the proposed NDA submission.*

ACTION ITEMS:

The Division will follow-up and provide feedback to the sponsor regarding a PPSR previously submitted in November 2006 (SN 289).

The meeting concluded at 2:10 pm.

_____/_____
Sharon Thomas Date
Project Manager
Minutes preparer

Concurrence Chair: _____/_____
Ramzi Dagher, M.D. Date
Medical Team Leader

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/s/

Ramzi Dagher
2/20/2007 03:49:08 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 58,546

Bristol-Myers Squibb Company
Attention: Albert Kraus, Ph.D.
Group Director, Global Regulatory Science
5 Research Parkway
Wallingford, CT 06512

Dear Dr. Kraus:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ixabepilone (BMS-247550).

We also refer to your November 23, 2004, request, serial number 173, for a special clinical protocol assessment, received November 24, 2004. The protocol is entitled "A Phase III Trial of a Novel Epothilone BMS-247550 plus Capecitabine Versus Capecitabine Alone in Patients with Advanced Breast Cancer Previously Treated with or Resistant to an Anthracycline and who are Taxane Resistant (CA163046)."

This Special Protocol Assessment was submitted in response to the Division's facsimile dated October 22, 2004, which provided comments regarding a protocol amendment made to CA163046. Below are the original comments from the October 22, 2004 FDA facsimile, immediately followed by the response provided in the November 23, 2004, and then immediately followed by the Division's responses.

Original FDA comment dated October 22, 2004

"The change in the Inclusion criterion number 5 (Page 42, Section 5.1) will require

-Stratifying patients at randomization by prior therapy in metastatic setting (yes/no)."

BMS response dated November 23, 2004

"We agree. The randomization will include an additional stratification factor of 'Prior therapy in a metastatic setting (yes/no).' Since all the patients who have entered the study prior to implementation of this amendment have received prior therapy in the metastatic setting, we will place these patients in the "Yes" category for this factor."

FDA Response:

This is acceptable.

Original FDA Comment dated October 22, 2004

"Using unadjusted log-rank test for protocol-specified primary endpoint analysis, as a stratified log-rank test can no longer be used."

BMS response dated November 23, 2004

"We recommend an alternate solution. We propose the protocol specified primary endpoint analysis to be a log rank test stratified by the 3 factors used in the randomization (excluding investigative site). We believe that the factors used in the randomization are prognostic and should be accounted for in the analysis. In particular, visceral disease in liver and/or lung has been shown to be a predictive covariate for progression-free survival and overall survival in metastatic breast cancer patients (Berruti et. al, Novarro et al). When structure has been imposed at randomization by stratification on factors known to be moderately predictive, performing an unstratified analysis may result in treatment comparisons with reduced power due to overestimation of variance and attenuation of treatment effect (Fleming and Lin). Additionally, this proposal is consistent with the ICH E9 guidance which states 'Factors on which randomization has been stratified should be accounted for later in the analysis.'

We will also incorporate the following unstratified analyses to further assist in the interpretation of the primary analyses:

- An unstratified log-rank test (as proposed by FDA).
- A Cox proportional hazards model with covariates representing treatment and the three stratification factors used in the randomization."

FDA Response:

This is acceptable.

Original FDA comment dated October 22, 2004

"Have you performed a comparative interim analysis? If so, then the overall type I error rate needs to be adjusted."

BMS response dated November 23, 2004

"A comparative interim analyses was performed for review by the independent Data Monitoring committee (DMC) to assess safety and evaluate risk/benefit for the patients based on the database of 02AUG04, when data was available for at least 2 cycles in the first 100 patients randomized. Another unscheduled interim analysis was performed at the request of the DMC based on the database of Oct 29th, 2004, to include all patients who were randomized on or before Sep 20th, 2004. Both analyses were performed by an independent statistician at BMS who provided the analyses for review only by the DMC and represented BMS at the DMC meetings. Although an interim analysis was performed, BMS was not provided access to the results of these analyses.

As described in the DMC charter, the nominal significance level for progression-free survival (the primary endpoint in this study) will be adjusted for all interim analyses using an O'Brien-Fleming spending function. There will be no adjustments for the significance levels of any of the secondary endpoints, to test for efficacy.

FDA Response:

We reiterate that the study should be powered to detect a difference in survival. Time to Progression and response rate data from patients with measurable disease may be acceptable to support Subpart H approval of BMS-247550 in patients who have been previously treated with an anthracycline and a taxane. Furthermore, a statistically significant difference in TTP may not necessarily demonstrate a clinically meaningful difference. We also suggest that you prioritize the sequence of testing of secondary endpoints and to maintain an overall type I error rate of .05 for testing secondary endpoints. We recognize that you have conducted an interim survival analysis and we suggest you adjust type I error rate for the final survival analysis.

Original FDA comment dated October 22, 2004

"Do you foresee a need to increase the size of the trial due to the changes in the patient population?"

BMS response dated November 23, 2004

"The final analysis for this trial is planned at the time when 615 disease progression-free events have been observed. We therefore do not foresee a need to increase the size of the trial because of the change in the patient population. In fact, we expect the difference in activity between the BMS-247550 + Capecitabine arm and the Capecitabine arm to be the same for patients who have received prior therapy in the metastatic settings vs. patients who have not received prior therapy in the metastatic setting. Additionally, we expect most of the patients eligible to be in the study (patients who are resistant to Taxane and who are either previously treated with or are resistant to Anthracycline) to have had prior therapy in the metastatic setting."

FDA Response:

This is acceptable.

Also, in your submission of November 23, 2004, you provided the Data Monitoring Committee Charter for protocol CA163046. The Division has completed its review of the Charter and have no comments.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our "*Guidance for Industry; Formal Meetings With Sponsors and Applicants for PDUFA Products*"). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at http://www.fda.gov/cder/guidance/index.htm. This meeting would

be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, call Amy Baird, Consumer Safety Officer, at (301) 594-5779.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Sharon Thomas
6/15/2007 04:43:59 PM
CSO