CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-065

OFFICE DIRECTOR MEMO

Division Director Summary Review of a New Drug Application

NDA: 22-065
Drug: Ixempra™ *Kit* (ixabepilone) for Injection
Applicant: Bristol-Myers Squibb Company
Date: October 15, 2007

This new drug application seeks approval of ixabepilone for the following 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. Anthracycline resistance is defined as progression while on therapy or within 6 months in the adjuvant setting or 3 months in the metastatic setting. Taxane resistance is defined as progression while on therapy or within 12 months in the adjuvant setting or 4 months in the metastatic setting.
>
> 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.

Ixabepilone is a semi-synthetic analog of epothilone B. Ixabepilone binds directly to β-tubulin subunits on microtubules, leading to suppression of microtubule dynamics. Ixabepilone suppresses the dynamic instability of αβ-II and αβ-III microtubules.

The safety and efficacy data supporting the approval of the application are summarized in the following excerpts from the draft package insert:

> In an open-label, multicenter, multinational, randomized trial of 752 patients with metastatic or locally advanced breast cancer, the efficacy and safety of Ixempra™ (40 mg/m^2 every 3 weeks) in combination with capecitabine (at 1000 mg/m^2 twice daily for 2 weeks followed by 1 week rest) were assessed in comparison with capecitabine as monotherapy (at 1250 mg/m^2 twice daily for 2 weeks followed by 1 week rest). Patients were previously treated with anthracyclines and taxanes. Patients were required to have demonstrated tumor progression or resistance to taxanes and anthracyclines as follows:
>
> - tumor progression within 3 months of the last anthracycline dose in the metastatic setting or recurrence within 6 months in the adjuvant or neoadjuvant setting, and

- tumor progression within 4 months of the last taxane dose in the metastatic setting or recurrence within 12 months in the adjuvant or neoadjuvant setting.

For anthracyclines, patients who received a minimum cumulative dose of 240 mg/m^2 of doxorubicin or 360 mg/m^2 of epirubicin were also eligible.

Sixty-seven percent of patients were White, 23% were Asian and 3% were Black. Both arms were evenly matched with regards to race, age (median 53 years), baseline performance status (Karnofsky 70-100%), and receipt of prior adjuvant or neo-adjuvant chemotherapy (75%). Tumors were ER-positive in 47% of patients, ER-negative in 43%, HER2-positive in 15%, HER2-negative in 61%, and ER-negative, PR-negative, HER2-negative in 25%. The baseline disease characteristics and previous therapies for all patients (n=752) are shown in Table 6.

Table 6: Baseline Disease Characteristics and Previous Therapies

	Ixempra™ with capecitabine n=375	**Capecitabine n=377**
Site of disease		
Visceral disease (liver or lung)	316 (84%)	315 (84%)
Liver	245 (65%)	228 (61%)
Lung	180 (48%)	174 (46%)
Lymph node	250 (67%)	249 (66%)
Bone	168 (45%)	162 (43%)
Skin/soft tissue	60 (16%)	62 (16%)
Number of prior chemotherapy regimens in metastatic setting[a]		
0	27 (7%)	33 (9%)
1	179 (48%)	184 (49%)
2	152 (41%)	138 (37%)
≥3	17 (5%)	22 (6%)
Anthracycline resistance[b]	164 (44%)	165 (44%)
Taxane Resistance[c]		
Neoadjuvant/adjuvant setting	40 (11%)	44 (12%)
Metastatic setting	327 (87%)	319 (85%)

[a] For TRADENAME plus capecitabine versus capecitabine only, prior treatment in the metastatic setting included cyclophosphamide (25% vs. 23%), fluorouracil (22% vs. 16%), vinorelbine (11% vs. 12%), gemcitabine (9% each arm), carboplatin (9% vs. 7%), liposomal doxorubicin (3% each arm), and cisplatin (2% vs. 3%).

[b] Tumor progression within 3 months in the metastatic setting or recurrence within 6 months in the adjuvant or neoadjuvant setting.

[c] 24% and 21% of patients had received 2 or more taxane-containing regimens in the combination and single agent treatment groups, respectively.

The patients in the combination treatment group received a median of 5 cycles of treatment and patients in the capecitabine monotherapy treatment group received a median of 4 cycles of treatment.

The primary endpoint of the study was progression-free survival (PFS) defined as time from randomization to radiologic progression as determined by Independent Radiologic Review (IRR), clinical progression of measurable skin lesions or death from any cause. Other study endpoints included objective tumor response based on Response Evaluation Criteria in Solid Tumors (RECIST), time to response, response duration, and overall survival. The data for overall survival analysis are not mature.

Ixempra™ in combination with capecitabine resulted in a statistically significant improvement in PFS compared to capecitabine monotherapy. The results of the study are presented in Table 7 and Figure 1.

Table 7: Efficacy of Ixempra™ in Combination with Capecitabine vs. Capecitabine Alone - Intent-to-Treat Analysis

Efficacy Parameter	**TRADENAME with Capecitabine n=375**	**Capecitabine n=377**
PFS		
Number of events[a]	242	256
Median	5.7 months	4.1 months
(95% CI)	(4.8 - 6.7)	(3.1 - 4.3)
Hazard Ratio[b] (95% CI)	0.69 (0.58 - 0.83)	
p-value[c] (Log rank)	<0.0001	
Objective Tumor Response Rate (95% CI)	34.7% (29.9 - 39.7)	14.3% (10.9 - 18.3)
p-value[c] (CMH)[d]	<0.0001	
Duration of Response, Median (95% CI)	6.4 months (5.6 - 7.1)	5.6 months (4.2 - 7.5)

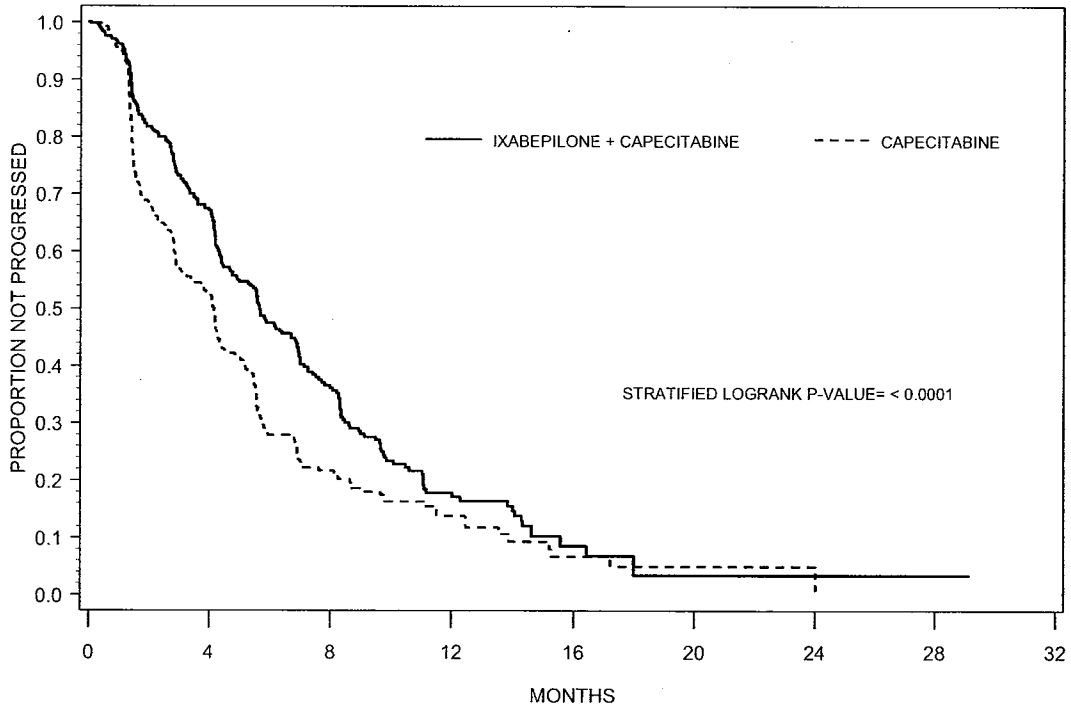
[a] Patients were censored for PFS at the last date of tumor assessment prior to the start of subsequent therapy. In patients where independent review was not available PFS was censored at the randomization date.

[b] For the hazard ratio, a value less than 1.00 favors combination treatment, CI adjusted for interim analysis.

[c] Stratified by visceral metastasis in liver/lung, prior chemotherapy in metastatic setting, and anthracycline resistance.

[d] Cochran-Mantel-Haenszel test

Figure 1: **Progression-free Survival Kaplan Meier Curves**



Ixempra™ was evaluated as a single agent in a multicenter single-arm study in 126 women with metastatic or locally advanced breast cancer. The study enrolled patients whose tumors had recurred or had progressed following two or more chemotherapy regimens including an anthracycline, a taxane, and capecitabine. Patients who had received a minimum cumulative dose of 240 mg/m^2 of doxorubicin or 360 mg/m^2 of epirubicin were also eligible. Tumor progression or recurrence were prospectively defined as follows:

- Disease progression while on therapy in the metastatic setting (defined as progression while on treatment or within 8 weeks of last dose),
- Recurrence within 6 months of the last dose in the adjuvant or neoadjuvant setting (only for anthracycline and taxane),
- HER2 positive patients must also have progressed during or after discontinuation of trastuzumab.

In this study the median age was 51 years (range, 30-78), and 79% were White, 5% Black, and 2% Asian, Karnofsky performance status was 70-100%, 88% had received two or more prior chemotherapy regimens for metastatic disease, and 86% had liver and/or lung metastases. Tumors were ER-positive in 48% of patients, ER-negative in 44%, HER2-positive in 7%, HER2-negative in 72%, and ER-negative, PR-negative, HER2-negative in 33%.

Ixempra™ was administered at a dose of 40 mg/m^2 intravenously over 3 hours every 3 weeks. Patients received a median of 4 cycles (range 1 to 18) of Ixempra™ therapy.

Objective tumor response was determined by independent radiologic and investigator review using RECIST. Efficacy results are presented in Table 8.

Table 8: Efficacy of Ixempra™ in Metastatic and Locally Advanced Breast Cancer

Endpoint	Result
Objective tumor response rate (95% CI)	
IRR Assessment[a] (N = 113)	12.4% (6.9 - 19.9)
Investigator Assessment (N = 126)	18.3% (11.9 - 27.0)
Time to response[b] (N = 14)	
Median, weeks (min - max)	6.1 (5 - 54.4)
Duration of response[b] (N = 14)	
Median, months (95% CI)	6.0 (5.0 - 7.6)

a All responses were partial.

b As assessed by IRR.

The most common adverse reactions (≥20%) reported by patients receiving Ixempra™ were peripheral sensory neuropathy, fatigue/asthenia, myalgia/arthralgia, alopecia, nausea, vomiting, stomatitis/mucositis, diarrhea, and musculoskeletal pain. The following additional reactions occurred in ≥20% in combination treatment: palmar-plantar erythrodysesthesia (hand-foot) syndrome, anorexia, abdominal pain, nail disorder, and constipation. The most common hematologic abnormalities (>40%) include neutropenia, leukopenia, anemia, and thrombocytopenia.

Table 4 presents non-hematologic adverse reactions reported in 5% or more of patients. Hematologic abnormalities are presented separately in Table 5.

Table 4: **Non-hematologic Drug-related Adverse Reactions Occurring in at Least 5% of Patients with Metastatic or Locally Advanced Breast Cancer Treated with Ixempra™**

	Study 046				Study 081	
	Ixempra™ with capecitabine n=369		Capecitabine n=368		Ixempra™ monotherapy n=126	
System Organ Class[a] / Preferred Term	Total (%)	Grade 3/4 (%)	Total (%)	Grade 3/4 (%)	Total (%)	Grade 3/4 (%)
Infections and Infestations						
Upper respiratory tract infection[b]	4	0	3	0	6	0
Blood and Lymphatic System Disorders						
Febrile neutropenia	5	4[c]	1	1[d]	3	3[d]
Immune System Disorders						
Hypersensitivity[b]	2	1[d]	0	0	5	1[d]
Metabolism and Nutrition Disorders						
Anorexia[b]	34	3[d]	15	1[d]	19	2[d]
Dehydration[b]	5	2	2	<1[d]	2	1[d]
Psychiatric						
Insomnia[b]	9	<1[d]	2	0	5	0
Nervous System Disorders						
Peripheral neuropathy						
Sensory neuropathy[b,c,e]	65	21	16	0	62	14
Motor neuropathy[b]	16	5[d]	<1	0	10	1[d]
Headache	8	<1[d]	3	0	11	0
Taste disorder[b]	12	0	4	0	6	0
Dizziness	8	1[d]	5	1[d]	7	0
Eye Disorders						
Lacrimation increased	5	0	4	<1[d]	4	0
Vascular Disorders						
Hot flush[b]	5	0	2	0	6	0
Respiratory, Thoracic, and						

Table 4: Non-hematologic Drug-related Adverse Reactions Occurring in at Least 5% of Patients with Metastatic or Locally Advanced Breast Cancer Treated with Ixempra™

	Study 046				Study 081	
	Ixempra™ with capecitabine n=369		Capecitabine n=368		Ixempra™ monotherapy n=126	
System Organ Class[a] / Preferred Term	Total (%)	Grade 3/4 (%)	Total (%)	Grade 3/4 (%)	Total (%)	Grade 3/4 (%)
Mediastinal Disorders						
Dyspnea[b]	7	1	4	1	9	1[d]
Cough[b]	6	0	2	0	2	0
Gastrointestinal Disorders						
Nausea	53	3[d]	40	2[d]	42	2[d]
Vomiting[b]	39	4[d]	24	2	29	1[d]
Stomatitis/mucositis[b]	31	4	20	3[d]	29	6
Diarrhea[b]	44	6[d]	39	9	22	1[d]
Constipation	22	0	6	<1[d]	16	2[d]
Abdominal pain[b]	24	2[d]	14	1[d]	13	2[d]
Gastroesophageal reflux disease[b]	7	1[d]	8	0	6	0
Skin and Subcutaneous Tissue Disorders						
Alopecia[b]	31	0	3	0	48	0
Skin rash[b]	17	1[d]	7	0	9	2[d]
Nail disorder[b]	24	2[d]	10	<1[d]	9	0
Palmar-plantar erythrodysesthesia syndrome[b,f]	64	18[d]	63	17[d]	8	2[d]
Pruritus	5	0	2	0	6	1[d]
Skin exfoliation[b]	5	<1[d]	3	0	2	0
Skin hyperpigmentation[b]	11	0	14	0	2	0
Musculoskeletal, Connective Tissue, and Bone Disorders						

Table 4: Non-hematologic Drug-related Adverse Reactions Occurring in at Least 5% of Patients with Metastatic or Locally Advanced Breast Cancer Treated with Ixempra™

	Study 046				Study 081	
	Ixempra™ with capecitabine n=369		Capecitabine n=368		Ixempra™ monotherapy n=126	
System Organ Class[a]/ Preferred Term	Total (%)	Grade 3/4 (%)	Total (%)	Grade 3/4 (%)	Total (%)	Grade 3/4 (%)
Myalgia/arthralgia[b]	39	8[d]	5	<1[d]	49	8[d]
Musculoskeletal pain[b]	23	2[d]	5	0	20	3[d]
General Disorders and Administrative Site Conditions						
Fatigue/asthenia[b]	60	16	29	4	56	13
Edema[b]	8	0	5	<1[d]	9	1[d]
Pyrexia	10	1[d]	4	0	8	1[d]
Pain[b]	9	1[d]	2	0	8	3[d]
Chest pain	4	1[d]	<1	0	5	1[d]
Investigations						
Weight decreased	11	0	3	0	6	0

a System organ class presented as outlined in Guidelines for Preparing Core Clinical Safety Information on Drugs by the Council for International Organizations of Medical Sciences (CIOMS).

b A composite of multiple MedDRA Preferred Terms.

c NCI CTC grading for febrile neutropenia ranges from Grade 3 to 5. Three patients (1%) experienced Grade 5 (fatal) febrile neutropenia. Other neutropenia-related deaths (9) occurred in the absence of reported febrile neutropenia (see *Warnings and Precautions* 5.2).

d No grade 4 reports.

e Peripheral sensory neuropathy (graded with the NCI CTC scale) was defined as the occurrence of any of the following: areflexia, burning sensation, dysesthesia, hyperesthesia, hypoesthesia, hyporeflexia, neuralgia, neuritis, neuropathy, neuropathy peripheral, neurotoxicity, painful response to normal stimuli, paresthesia, pallanesthesia, peripheral sensory neuropathy, polyneuropathy, polyneuropathy toxic and sensorimotor disorder.

Peripheral motor neuropathy was defined as the occurrence of any of the following: multifocal motor neuropathy, neuromuscular toxicity, peripheral motor neuropathy, and peripheral sensorimotor neuropathy.

f Palmar-plantar erythrodysesthesia (Hand-food syndrome) was graded on a 1-3 severity scale in Study 046.

Table 5: Hematologic Abnormalities in Patients with Metastatic or Locally Advanced Breast Cancer Treated with Ixempra™

	Study 046				Study 081	
	TRADENAME with capecitabine n=369		Capecitabine n=368		TRADENAME monotherapy n=126	
Hematology Parameter	Grade 3 (%)	Grade 4 (%)	Grade 3 (%)	Grade 4 (%)	Grade 3 (%)	Grade 4 (%)
Neutropenia[a]	32	36	9	2	31	23
Leukopenia (WBC)	41	16	5	1	36	13
Anemia (Hgb)	8	2	4	1	6	2
Thrombocytopenia	5	3	2	2	5	2

[a] G-CSF (granulocyte colony stimulating factor) or GM-CSF (granulocyte macrophage stimulating factor) was used in 20% and 17% of patients who received TRADENAME in Study 046 and Study 081, respectively.

The following serious adverse reactions were also reported in 1323 patients treated with TRADENAME as monotherapy or in combination with other therapies in Phase 2 and 3 studies.

Infections and Infestations: sepsis, pneumonia, infection, neutropenic infection, urinary tract infection, bacterial infection, enterocolitis, laryngitis, lower respiratory tract infection

Blood and Lymphatic System Disorders: coagulopathy, lymphopenia

Metabolism and Nutrition Disorders: hyponatremia, metabolic acidosis, hypokalemia, hypovolemia

Nervous System Disorders: cognitive disorder, syncope, cerebral hemorrhage, abnormal coordination, lethargy

Cardiac Disorders: myocardial infarction, supraventricular arrhythmia, left ventricular dysfunction, angina pectoris, atrial flutter, cardiomyopathy, myocardial ischemia

Vascular Disorders: hypotension, thrombosis, embolism, hemorrhage, hypovolemic shock, vasculitis

Respiratory, Thoracic, and Mediastinal Disorders: pneumonitis, hypoxia, respiratory failure, acute pulmonary edema, dysphonia, pharyngolaryngeal pain

Gastrointestinal Disorders: ileus, colitis, impaired gastric emptying, esophagitis, dysphagia, gastritis, gastrointestinal hemorrhage

Hepatobiliary Disorders: acute hepatic failure, jaundice

Skin and Subcutaneous Tissue Disorders: erythema multiforme

Musculoskeletal, Connective Tissue Disorders, and Bone Disorders: muscular weakness, muscle spasms, trismus

Renal and Urinary Disorders: nephrolithiasis, renal failure

General Disorders and Administration Site Conditions: chills

Investigations: increased transaminases, increased blood alkaline phosphatase, increased gamma-glutamyltransferase.

Peripheral neuropathy was common and occurred early during treatment; 75% of new onset or worsening neuropathy occurred during the first 3 cycles. In the clinical studies, peripheral neuropathy was managed through dose reductions, dose delays and treatment discontinuation. Neuropathy was the most frequent cause of treatment discontinuation due to drug toxicity. In Studies 046 and 081, 80% and 87%, respectively, of patients with peripheral neuropathy who received Ixempra™ had improvement or no worsening of their neuropathy following dose reduction. For patients with grade 3/4 neuropathy in Studies 046 and 081, 76% and 79%, respectively, had documented improvement to baseline or grade 1, twelve weeks after onset.

Table 1: Treatment-related Peripheral Neuropathy

	TRADENAME with capecitabine Study 046	**TRADENAME as monotherapy Study 081**
Peripheral neuropathy (all grades)[a,b]	67%	63%
Peripheral neuropathy (grades 3/4)[a,b]	23%	14%
Discontinuation due to neuropathy	21%	6%
Median number of cycles to onset of grade 3/4 neuropathy	4	4
Median time to improvement of grade 3/4 neuropathy to baseline or to grade 1	6.0 weeks	4.6 weeks

[a] Sensory and motor neuropathy combined.

[b] 24% and 27 % of patients in 046 and 081. respectively had preexisting neuropathy (grade 1).

A pooled analysis of 945 cancer patients treated with Ixempra™ indicated that patients with diabetes mellitus may be at increased risk of severe neuropathy. The presence of grade 1 neuropathy and prior therapy with neurotoxic chemotherapy agents did not predict either the development or worsening of neuropathy. Patients with moderate to severe neuropathy (grade 2 or greater) were excluded from studies with Ixempra™.

Myelosuppression was dose-dependent and primarily manifested as neutropenia. Grade 4 neutropenia (<500 cells/mm^3) occurred in 36% of patients treated with Ixempra™ in combination with capecitabine and 23% of patients treated with Ixempra™ monotherapy. Febrile neutropenia and infection with neutropenia were reported in 5% and 6% of patients treated with Ixempra™ in combination with capecitabine, respectively, and 3% and 5% of patients treated with Ixempra™ as monotherapy, respectively. Neutropenia-related death occurred in 1.9% of 414 patients with normal hepatic function or mild hepatic impairment treated with Ixempra™ in combination with capecitabine. The rate of neutropenia-related deaths was higher (29%, 5 out of 17) in patients with AST or ALT >2.5 x ULN or bilirubin >1.5 x ULN. Neutropenia-related death occurred in 0.4% of 240 patients treated with TRADENAME as monotherapy. No neutropenia-related deaths were reported in 24 patients with AST or ALT >2.5 x ULN or bilirubin >1.5 x ULN treated with Ixempra™ monotherapy.

The frequency of cardiac adverse reactions (myocardial ischemia and ventricular dysfunction) was higher in the TRADENAME in combination with capecitabine (1.9%) than in the capecitabine alone (0.3%) treatment group. Supraventricular arrhythmias were observed in the combination arm (0.5%) and not in the capecitabine alone arm.

Clinical Review

The Clinical Review by Drs. Robert Lechleider and Edvardas Kaminskas made the following recommendation on regulatory action:

The reviewers recommend on the basis of this review of NDA 22-065 that ixabepilone (Ixempra™) receive regular approval for the following indications:

- 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. Anthracycline resistance is defined as progression while on therapy or within 6 months in the adjuvant setting or 3 months in the metastatic setting. Taxane resistance is defined as progression while on therapy or within 12 months in the adjuvant setting or 4 months in the metastatic setting.
- As monotherapy for the treatment of metastatic or locally advanced breast cancer patients whose tumors are resistant or refractory to an anthracycline, a taxane, and capecitabine.

The review did not recommend risk management activities beyond standard post-marketing surveillance. The following Phase 4 commitments were recommended:

- To submit the complete study report and datasets for the ongoing clinical study CA163048 "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.

- 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.

The Medical Team Leader Review by Ramzi Dagher, M.D., made the following recommendation:

> I agree with the medical reviewers' recommendation for regular approval of ixabepilone for the following indications:
>
> TRADENAME 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. Anthracycline resistance is defined as progression while on therapy or within 6 months in the adjuvant setting or 3 months in the metastatic setting. Taxane resistance is defined as progression while on therapy or within 12 months in the adjuvant setting or 4 months in the metastatic setting.
>
> TRADENAME 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.

Clinical Inspection Summary

Two clinical study sites and the applicant were inspected. In addition, a trade complaint was also evaluated. The Clinical Inspection Summary provided the following overall assessment of findings:

> 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.
>
> DDOP clinical reviewers' evaluation of the 10/5/07 Trade Complaint letter concerning this investigational product concluded that the information provided by the complainant had no impact on the outcome of the review and evaluation of the clinical data or approvability of this NDA application.

Statistical Review and Evaluation

The Statistical Review and Evaluation by Dr. Xiaoping Jiang provided the following conclusions and recommendations:

> In this reviewer's opinion, based on the materials submitted for this NDA, the results from the study CA163046 support the sponsor's claim that ixabepilone and capecitabine administered as combination therapy demonstrated statistically significant improvements in progression free survival (PFS) over capecitabine alone for the patients with advanced breast cancer previously treated with or resistant to an anthracycline and who are taxane resistant. Based on independent radiology review committee (IRRC) assessment, the estimated median PFS is 5.65 months for combination treatment of Ixabepilone and capecitabine versus 4.10 months for capecitabine treatment alone (stratified log-rank p-value<0.0001). As of database lock (01-Dec-2006), 483 patients had died. The sponsor has reported that at the unscheduled interim analysis of OS with at least 483 deaths, no statistical difference was observed. Whether Ixabepilone shows survival benefit as a combination therapy for the patients will depend on the survival results when data are mature. The final analysis of OS will be conducted when 631 patients have died as specified in the protocol.
>
> The sponsor claimed the effectiveness of ixabepilone as monotherapy was supported by the results of the single-arm study CA163081 and based on the object response rate (ORR) per the IRRRC assessment. No statistical comparison

was conducted in study CA163081 and therefore no statistical inference will be drawn from the study. The sponsor claimed that ixabepilone administered as a single agent demonstrated clinical activity in patients with metastatic or locally advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. Per sponsor, the observed IRRC ORR was 11.9% in 126 treated patients and the estimated median duration of response was 6.3 months. FDA's estimated median duration of response is 5.3 months. Whether its effectiveness is adequate for approval of ixabepilone as monotherapy for the proposed indication will be determined by clinical judgment.

Clinical Pharmacology Review

The Clinical Pharmacology Review by Dr. Julie Bullock stated that "This NDA is considered acceptable from a clinical pharmacology perspective." The review recommended labeling recommendations regarding dose modifications for hepatic impairment and revisions to the Drug Interactions section (7) and to the Renal Impairment section (8.7). The review recommended three Phase 4 commitments:

1. Submit the completed report for the rifampin drug-drug interaction evaluation and datasets for study CA163102.

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

3. The potential for ixabepilone to affect the QT interval needs to be investigated.

Pharmacology/Toxicology Review and Evaluation

The Pharmacology/Toxicology Review and Evaluation by Dr. Robeena Aziz made the following recommendations:

A. Recommendation on approvability

Approvable. The non-clinical studies with intravenous infusion of ixabepilone support the safety of its use in metastatic breast cancer.

B. Recommendation for nonclinical studies

No additional non-clinical studies are required for ixabepilone

C. Recommendations on labeling

The recommendations to the sponsor's proposed labeling are given, with a detailed report regarding the rationale for the recommended changes, in a subsequent review.

The Supervisory Pharmacologist memorandum by John Leighton, Ph.D. made the following recommendation: "I concur with Dr. Aziz's conclusion that pharmacology and toxicology data support the approval of NDA 22-065, ixabepilone. There are no outstanding nonclinical issues related to the approval of ixabebilone."

Chemistry Review

The Chemistry Review by Dr. Ravindra Kasliwal made the following recommendation and conclusion on approvability:

The application is recommended for an approval action for chemistry, manufacturing and controls under section 505 of the Act, provided an acceptable recommendation has been received form product quality microbiology, and the trademark acceptability has been determined by Office of drug safety. The Office of Compliance recommeds that the manufacturing facilities are acceptable as of 10-Sep-2007.

The review made the following comments regarding on Phase 4 agreements:

The company has also indicated that the representative certificates of analysis for polyoxyethylated castor oil, purified and dehydrated alcohol will be provided at a later date. The COAs have not been received as of the date of this review. The coamny *(sic)* should also be reminded of this issue.

Product Quality Microbiology Review

The microbiology review by Dr. Vinayak Pawar stated that "The application is recommended for approval from microbiology product quality standpoint."

DSRCS Review of Patient Labeling

The DSRCS review of patient labeling was conducted by Sharon Mills, BSN, RN, CCRP. The recommendations were discussed during labeling meetings and most were incorporated into the PPI.

DMETS Review of Proprietary Name, Label, and Labeling

DMETS did not object to the proposed proprietary name of Ixempra™. However, DMETS had a number of recommendations to minimize potential errors with the use of the product. All but the following recommendation were addressed during the labeling negotiations. This recommendation will be addressed as a phase 4 commitment.

> DMETS recommends the drug vial and diluent be physically linked together in some manner. We recognize the vials are contained in a single carton. However, this may not be adequate to ensure the diluent and vial are not separated due to space constraints in the refrigerator. The use of plastic rings binding both products may lessen the likelihood of storage of the drug and diluent in different places and avert the possibility of not using this diluent or use of an inappropriate diluent.

DDMAC Review of Draft Labeling

The DDMAC Review of Draft Labeling was performed by Kathy Oh. The comments were discussed and incorporated where appropriate during internal labeling meetings.

Oncologic Drugs Advisory Committee

This application was not taken to a meeting of the Oncologic Drugs Advisory Committee. The Office of Oncology Drug Products has accepted the endpoint of progression-free survival as an approval endpoint and the toxicity profile is similar to that of other cytotoxic drugs.

Conclusion

I concur with the reviewers' recommendations that the application should be approved. Ixabepilone in combination with capecitabine in the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer was taxane resistant and for whom further anthracycline therapy was contraindicated resulted in a significantly prolonged progression-free survival and an increased objective response rate compared to capecitabine alone. Although this efficacy was achieved at a cost of increased toxicity, particularly peripheral neuropathy and myelosuppression, this patient population is in need of treatment options. The survival data are not mature. However, the DSMB did not stop the trial based on an interim analysis of survival that was conducted at the time of the PFS analysis. As noted below, submission of the final survival analysis for the combination study is a phase 4 commitment. I also concur with the recommendation for approval of ixabepilone for the indication of monotherapy in the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine. This patient population currently has no approved therapies.

The applicant has agreed to the following phase 4 commitments:

1. 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 the prespecified number of events (deaths), or earlier if recommended by the independent data monitoring committee.

   Protocol Submission: June 2, 2003
   Study Start: November 11, 2003
   Final Report Submission: December 2008

2. 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.

   Protocol Submission: June 2, 2003
   Study Start: September 4, 2003
   Final Report Submission and Datasets: October 2008

3. Submit the completed report for the rifampin drug-drug interaction evaluation and datasets for study CA163102.

Protocol Submission: July 12, 2005
Study Start: September 28, 2005

Final Submission Report: September 2009

4. An *in-vitro* assessment to determine if ixabepilone is a P-glycoprotein substrate or inhibitor needs to be conducted.

   Protocol Submission: Not applicable
   Study Start: April 2007

   Final Submission Report: September 2009

5. 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

6. Submit a packaging amendment to physically link the drug vial and diluent vial.

   Protocol Submission: October 2008
   Packaging Amendment Submission: October 2009

Recommended Regulatory Action

Agreement has been reached on the labeling and the post-marketing commitments. There are no outstanding issues. The application should be approved.

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Office of New Drugs
Center for Drug Evaluation and Research

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Robert Justice
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MEDICAL OFFICER

Richard Pazdur
10/15/2007 11:47:35 AM
MEDICAL OFFICER