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RESEARCH**

APPLICATION NUMBER:

205353Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo for Regulatory Action

Date	Electronic stamp date
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA #	205353
Applicant Name	Novartis Pharmaceuticals Corporation
Date of Submission	March 24, 2014
PDUFA Goal Date	November 24, 2014 (Major amendment extended to 02/24/15)
Proprietary Name (established name)	Farydak (panobinostat)
Dosage Forms / Strength	10 mg, 15 mg, and 20 mg capsules
Proposed Indications	FARYDAK, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma who have received at least 1 prior therapy
Action:	<i>Accelerated Approval</i>

Material Reviewed/Consulted	
OND Action Package, including:	
Deputy Division Director	Edvardas Kaminskas, MD
Regulatory Project Manager	Diane Hanner
Medical Officer Review	Barry W. Miller, MSN, CRNP/Adam George, PharmD/Nicole Gormley, MD, PhD/Virginia E. Kwitkowski, MS, RN, ACNP-BC.
Statistical Review	Chia-Wen Ko, PhD/Lei Nie, PhD/Rajeshwari Sridhara, PhD
Pharmacology Toxicology Review	Emily Place, PhD, MPH/Kimberly Ringgold, PhD/Haleh Saber, PhD/John K. Leighton, PhD
CMC Review/Biopharmaceutics Review/Product Quality Microbiology Review	Danuta Gromek-Woods, PhD/Ali H. Al Hakim, PhD/Elsbeth G. Chikhale, PhD/Angelica Dorantes, PhD/Erica Pfeiler, PhD
Clinical Pharmacology and Pharmacometrics Review	Joseph Grillo, PharmD/Sarah Dorff, PhD/Bahru Habtemariam, PharmD/Lian Ma, PhD/Nitin Mehrota, PhD/Ping Zhao, PhD
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OND=Office of New Drugs
 OMP=Office of Medical Policy
 DMPP=Division of Medical Policy Programs
 OPDP=Office of Prescription Drug Promotion
 OSE= Office of Surveillance and Epidemiology
 OMEPRM=Office of Medication Error Prevention and Risk Management
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK=Division of Risk Management
 OSI=Office of Scientific Investigations
 DGCP=Division of Good Clinical Practice Compliance
 CDTL=Cross-Discipline Team Leader

1. Introduction and Background

On March 24, 2014, Novartis Pharmaceuticals submitted NDA 205353 for panobinostat (a histone deacetylase inhibitor) in combination with bortezomib and dexamethasone, for the treatment of patients with multiple myeloma (MM), who have received at least 1 prior therapy.

Multiple myeloma is a malignant condition of plasma cells that leads to a monoclonal gammopathy. The proliferation of clonal plasma cells in the bone marrow leads to high levels of circulating monoclonal-M-immunoglobulin (referred to as “M-protein”). The clinical manifestations of MM include hypercalcemia, renal dysfunction, anemia, and bone lytic lesions.

Multiple myeloma accounts for approximately 1% of all cancers and 10% of hematologic malignancies. An estimated 24,000 new cases of MM will occur in the U.S. in 2014 with an estimated 11,000 deaths. The diagnosis is most common in the 6th and 7th decades of life and approximately 75% of patients are over 70 years of age. Blacks account for twice as many new cases of MM than Whites: 12.2 vs. 5.6 per 100,000 men and women per year (Howlader N, 2013).

There are two precursor conditions that can evolve into MM: monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma. These conditions are characterized by the presence of abnormal plasma cells in the marrow, presence of an M-protein, but without the clinical manifestations (Benjamin M. Cherry, 2013). Patients with MGUS and smoldering MM are estimated to have an average annual risk of transformation to MM of 1% and 10% per year, respectively (Kyle RA, 2010). There are no approved therapies for either MGUS or smoldering MM.

Treatment of newly diagnosed MM is typically initiated when the patient becomes symptomatic. The treatment of symptomatic MM depends on their risk stratification and whether the patient is fit enough to be a candidate for autologous stem-cell transplantation (ASCT). Responses to primary therapy are often transient, and MM is not considered curable with the available treatments. Patients who have relapsed or failed to respond to both bortezomib and immunomodulatory drugs generally have a poor prognosis with a median OS of only 9 months, regardless of salvage regimen (Kumar SK, 2012).

Table 1. FDA Approvals for Relapsed Multiple Myeloma

Drug Name <i>Indication</i>	Trial Type	Approval Date & Type	Approval Basis
Velcade (bortezomib)- <i>3rd line MM</i>	Single arm trial (n=256)	2003 <i>Accelerated</i>	ORR 28%
Velcade (bortezomib)- <i>2nd line MM</i>	RCT of Velcade vs. dexamethasone (n=669)	2005 <i>Regular</i>	Median TTP: Velcade 6.2 m vs. dex 3.5 m ΔTTP 2.7 m
Revlimid (lenalidomide)- <i>2nd line MM, in combination with dexamethasone</i>	Two RCTs of Revlimid + dex vs. dexamethasone alone (n=341, n=351)	2006 <i>Accelerated*</i>	Trial 1: Median TTP: Rev+dex 8.5m vs. dex 4.6m Δ TTP 3.9 m Trial 2: Median TTP Rev+dex NE vs. dex 4.6 m
Doxil (doxorubicin HCL liposome)- <i>2nd line MM (no prior Velcade)</i>	RCT of Doxil + bortezomib vs. bortezomib alone (n=646)	2007 <i>Regular</i>	Median TTP: Doxil+bort 9.3 m vs. bort 6.5 m. Δ TTP 2.8 m.
Kyprolis (carfilzomib)- <i>3rd line MM</i>	Single arm trial (n=266)	2012 <i>Accelerated</i>	ORR (sCR, CR, VGPR, PR): 23%. mDOR: 7.8m
Pomalyst (pomalidomide)- <i>3rd line MM</i>	RCT of Pomalyst + dex vs. Pomalyst alone (n=221)	2013 <i>Accelerated*</i>	PFS not evaluable; ORR (PR, CR): 29% vs. 7%. mDOR for Pom+dex: 7.4 m.

*Remains under Subpart H because it has a restricted distribution program
 bort = bortezomib, dex = dexamethasone, mDOR = median duration of response, m = months,
 MM = multiple myeloma, NE = not evaluable, ORR = overall response rate, pred = prednisone,
 RCT = randomized controlled trial, TTP = time to progression, Δ = difference

The FDA has previously granted approval for a second-line MM indication to three drugs: bortezomib (2005), lenalidomide (2005), and liposomal doxorubicin (2007). Carfilzomib and pomalidomide were granted a 3rd line indication under the accelerated approval regulations. In addition to these three products, cyclophosphamide (1959), melphalan (1964), and carmustine (1977) have broad indications for the treatment of patients with MM. Bortezomib, lenalidomide, and liposomal doxorubicin were all granted their approvals in this indication based upon randomized, controlled trials. Prior approvals were based upon doublet therapies (adding on to single-agents), whereas this application is of triplet therapy (bortezomib + dexamethasone ± panobinostat).

2. CMC/Device

There are no outstanding issues that would preclude approval from a CMC perspective. Panobinostat lactate anhydrous is slightly soluble in water; solubility is pH-dependent. Based on drug product stability data, the expiration period for panobinostat capsules is 36 months.

CMC reviewers have provided an overall acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable.

3. Nonclinical Pharmacology/Toxicology

There are no outstanding issues from a nonclinical perspective that would preclude approval. Panobinostat promoted cell death and cell cycle arrest *in vitro*, including human MM cells. Panobinostat also promoted cell death in MM cells from patients *ex vivo* and in both xenograft and disseminated mouse models of myeloma. Panobinostat in combination with bortezomib and dexamethasone had higher activity in reducing tumor burden and increasing survival compared to controls.

Panobinostat-related toxicities in rats and/or dogs are following: thyroid toxicities, decreased WBCs and platelets, hemorrhage in multiple organs including brain and lungs, inflammation in multiple organs including liver and lungs, bone marrow abnormalities including plasmacytosis and hyperostosis, skin hyperplasia and papilloma, and toxicities in male reproductive organs. Panobinostat and/or its metabolites crossed the blood-brain barrier in tissue distribution studies. Safety pharmacology studies further showed potential for CNS effects as indicated by reduced motor activity, wobbly gait, convulsions and reduced grip strength. QTc prolongation was observed in dogs.

Panobinostat was genotoxic in the battery of genetic toxicology studies and was teratogenic in rats and rabbits. In fertility studies, mating index, fertility index and conception rate were reduced. Increased resorption and post-implantation loss and reduced numbers of embryos were noted. Pregnancy Category D is recommended for FARYDAK.

4. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review team in their review concluded:

- The results of the Phase 1b dose escalation trial and the registration trial show that 73% of patients had dose interruptions or modifications, 87% experienced Grade 3/4 adverse events, and 33% were hospitalized due to adverse events. These were significantly higher in the panobinostat arm than in the control arm. The efficacy advantage was modest. Due to lack of dose/exposure-response data for efficacy, it is not possible to determine if a lower starting dose would provide similar efficacy and a better benefit-risk profile.
- A dose modification is required in patients with mild or moderate hepatic impairment. In patients with mild or moderate hepatic impairment AUC_{0-inf} increased by 43% and 105% compared to patients with normal hepatic function. A specific dose cannot be recommended because there is no reference dose available as discussed above. There was insufficient PK data in patients with severe hepatic impairment to make a reliable comparative PK assessment.

- Appropriate dose for patients taking a strong CYP3A inhibitor or inducer. Co-administration of FARYDAK 20 mg with a strong CYP3A4 inhibitor (ketoconazole) increases the C_{max} and AUC_{0-48} by 67% and 73%, respectively, suggesting that one-half the dose (10 mg) will provide comparable systemic exposure as 20 mg in the absence of CYP3A4 inhibitors. The sponsor did not characterize the influence of CYP3A4 inducers on the PK of panobinostat. A simulation study suggests that panobinostat exposure could be reduced by approximately 70% in the presence of CYP3A4 inducers.

The Office of Clinical Pharmacology has determined that the sponsor has not identified acceptable dose in this NME NDA to support a recommendation of approval of FARYDAK. In a review addendum on 01/23/2015, the Clinical Pharmacology Team deferred the recommendation of approvability of this NDA to the clinical review team and recommended two PMRs.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical-Efficacy

Efficacy and safety of panobinostat was evaluated in one randomized trial (LBH589D2308) and two single-arm trials (a Phase 1b dose finding study of panobinostat and bortezomib in patients with MM and a Phase 2 single-arm trial of panobinostat and bortezomib and dexamethasone in 55 patients with relapsed and bortezomib-refractory MM).

Trial D2308 was a large, international, randomized (1:1), double-blinded, placebo-controlled trial in which 768 subjects with relapsed MM were treated with bortezomib and dexamethasone with or without panobinostat. Patients with 1 to 3 prior treatments were eligible. The primary efficacy endpoint was investigator-assessed progression-free survival (PFS). The key secondary endpoint was OS. Randomization was stratified by the number of prior lines of therapy and by prior use of bortezomib. The patients were to be treated for a maximum of 48 weeks in two 24-week phases.

Enrollment in this trial occurred primarily in European (43%) and Asian (29%) countries; only 7% of subjects were from the U.S. The median age was 63 years (range, 28 to 84), 42% of patients were older than 65. Most of the subjects were White (about 65% in both arms), 30% were Asian, 3% blacks. Male/female distribution was 53%/47%. The median time from diagnosis was about 3 years. The median number of prior treatments was 1 (range, 1 – 4), 48% of patients had received 2 or 3 prior lines of therapy, 57% had prior stem cell transplantation. The most common agents were corticosteroids (90%), melphalan (80%), thalidomide (53%), cyclophosphamide (47%), bortezomib (44%), and lenalidomide (19%). Approximately 67% of subjects had mild or moderate renal impairment; approximately 93% had ECOG Performance Score of 0 – 1.

During an internal audit while the trial was on-going but after all subjects had completed treatment, the Applicant found that alternative methods for measuring M-protein, a key component of the response criteria, had been used in 25% of subjects on the panobinostat + BD arm and in 26% of subjects in the placebo + BD arm. An independent review committee (IRC) was established to assess the response data to be included in the results as non-prespecified sensitivity analysis.

Approximately 40 – 50% of subjects completed 24 weeks of treatment and approximately 26%, 48 weeks of treatment. Twice as many subjects discontinued treatment because of adverse events in the panobinostat arm (34% vs. 17%), and twice as many subjects discontinued treatment in the placebo arm because of disease progression (40% vs. 21%).

Efficacy Results in the Overall Trial Population

The results for the primary efficacy endpoint (PFS) are shown in Table 2 below. The difference between median PFS in the two arms as assessed by investigator was 3.9 months: 12.0 months in the panobinostat + BD arm vs. 8.1 months in the placebo + BD arm. The hazard ratio was 0.63 (95% CI: 0.52, 0.76), p-value <0.0001. In patients without M-protein measurement by protein electrophoresis, the investigators could only make a determination of 'progressive disease' or 'unknown response'.

Table 2. PFS by Investigator

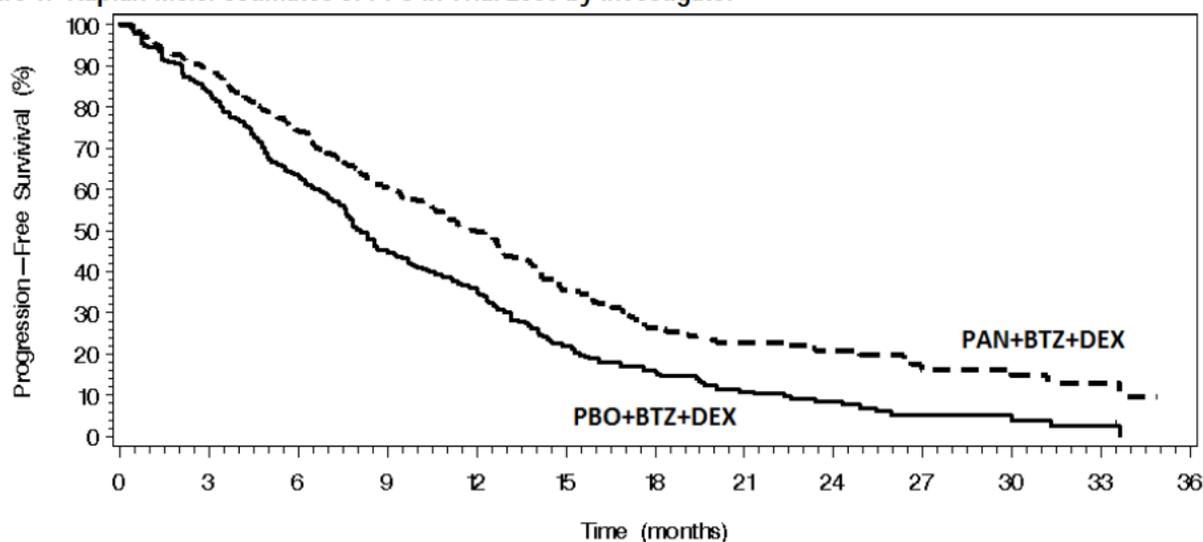
	Panobinostat + BD n=387	Placebo + BD n=381
PFS events, n	207 (53.5%)	260 (68.2%)
Censored, n	180 (46.5%)	121 (31.8%)
Median time to event, months ¹	12.0 (10.3, 12.9)	8.1 (7.6, 9.2)
Hazard ratio, 95% CI	0.63 (0.52, 0.76)	
p-value	<0.0001	

BD = bortezomib + dexamethasone, CI = confidence interval

¹Kaplan-Meier estimates

[Source: FDA analysis]

Figure 1. Kaplan-Meier estimates of PFS in Trial 2308 by Investigator



	Number of patients at risk												
	0	3	6	9	12	15	18	21	24	27	30	33	36
PAN+BTZ+DEX	387	268	202	153	113	76	52	38	26	14	10	5	0
PBO+BTZ+DEX	381	263	185	126	89	51	32	20	12	5	3	1	0

As noted in Table 2, there was very extensive censoring in both arms, 46.5% of patients in the panobinostat +BD arm and 31.8% of patients in the placebo + BD arms were censored. Censoring occurred more often in the panobinostat + BD arm, mostly due to incomplete or missing assessments and to patient withdrawal.

PFS analysis as determined by the IRC showed a median PFS of 9.9 months in the panobinostat + BD arm and 7.7 months in the placebo + BD arm, a difference of 2.2 months.

The data were not mature for the first secondary endpoint of OS at interim analysis, but the difference was not statistically significant between arms. The second secondary endpoint of Overall Response Rate showed higher response rates in the panobinostat + BD arm than in the placebo + BD arm in both investigator assessment (61% vs. 55%) and the IRC assessment (64% vs. 54%). About 11% of patients in the panobinostat + BD arm had a CR as compared to 6% in the placebo +BD arm. Median durations of response were 13.1 months and 10.9 months, favoring the panobinostat arm.

The FDA reviewers concluded that there is an improvement in PFS of uncertain magnitude, no difference in OS, a modestly increased ORR in the panobinostat + BD arm, and also a greater proportion of patients who dropped out in the panobinostat + BD arm due to adverse events, resulting in increased censored observations. Moreover, the safety profile in the panobinostat-containing arm was substantially worse in several adverse event categories. The Oncology Drugs Advisory Committee (ODAC) also did not feel that patients in the overall ITT population had a positive benefit/risk assessment for panobinostat added to BD.

Efficacy Results in a Prespecified Subgroup

The Applicant identified a protocol-specified subgroup of patients who had received prior treatment with both bortezomib and an immunomodulatory agent (n=193) as supporting a more favorable benefit/risk determination. Compared to the overall trial population, this subgroup had a larger percentage of patients from the United States (15%), was younger with a median age of about 60 years, 31% of patients in the panobinostat + BD arm and 38% in the placebo + BD arm were 65 years or older, and had a similar percentage in regard to race and gender as the ITT population. The median number of prior treatments was 2.

The key efficacy findings for this subset of patients are shown in Tables 3 and 4 and Figure 2. The difference in median PFS was 4.8 months, favoring the panobinostat + BD arm. This result is consistent with the statistically significant difference between arms in the overall population. There is a reduction in the percentage of censored events in this subgroup as compared to the overall population; however, the imbalance in censoring between the two arms persists, with a greater amount of censoring in the panobinostat + BD arm.

Table 3. Investigator-assessed PFS analysis of Trial D2308: Prior bortezomib and an immunomodulatory agent

	Panobinostat + BD n=94	Placebo + BD n=99
PFS events, n	57 (60.6%)	72 (72.7%)
Censored ¹ , n	37 (39.4%)	27 (27.3%)
Median time to event, months (95% CI)	10.6 (7.6, 13.8)	5.8 (4.4, 7.1)
Hazard ratio ² (95% CI)	0.56 (0.39, 0.79)	
p-value ³	0.0005	

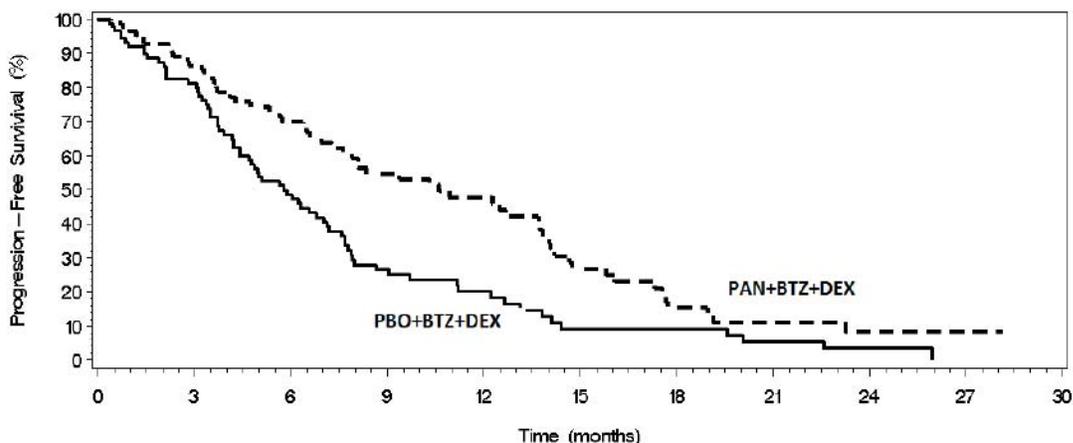
BD = bortezomib + dexamethasone, CI = confidence interval

¹ Censored for no event, next therapy, or ≥2 missing assessments prior to event documentation

² Estimated using Cox model stratified by randomization factors

³ Calculated based on log-rank test, stratified by the randomization factors

Figure 2. K-M plot of investigator-assessed PFS from Trial D2308 subgroup: prior bortezomib and an immunomodulatory agent



PAN+BTZ+DEX	94	68	46	33	25	14	8	4	3	1	0
PBO+BTZ+DEX	99	65	37	18	11	5	5	3	2	0	0

PAN+BTZ+DEX = panobinostat, bortezomib, and dexamethasone arm
 PBO+BTZ+DEX = placebo, bortezomib, and dexamethasone arm

The difference between arms in overall response rate (17%) is greater in this subgroup than in the overall trial population, as shown in Table 4. The median duration of response was greater in the panobinostat + BD arm than in the placebo + BD arm, as it was in the overall population.

Table 4 Response rate and duration of response in Trial D2308 subgroup: Prior bortezomib and an immunomodulatory agent

	Panobinostat + BD n=94	Placebo + BD n=99
Overall response rate ¹	55 (58.5%)	41 (41.4%)
95% CI	(48.6, 68.5)%	(31.7, 51.1)%
Complete response	8 (8.5%)	2 (2.0%)
Near complete response	13 (13.8%)	7 (7.1%)
Partial response	34 (36.2%)	32 (32.3%)
Median DOR, months	12.0	8.3
95% CI	9.7, 13.9	6.1, 12.3

BD = bortezomib + dexamethasone

7. Safety

Safety was evaluated in 758 patients with relapsed MM who were treated with panobinostat-bortezomib-dexamethasone or placebo-bortezomib-dexamethasone. The most common adverse reactions (>20%) on the panobinostat-containing arm were diarrhea, fatigue, nausea, peripheral edema, decreased appetite, pyrexia, and vomiting. Serious adverse reactions included pneumonia, diarrhea, thrombocytopenia, fatigue, and sepsis. There was an increased incidence in deaths not due to progressive disease (7% vs. 3.2%) on the panobinostat-containing arm.

The most common hematologic abnormalities included thrombocytopenia and neutropenia; the most common chemistry abnormalities were hypophosphatemia and hypokalemia. ECG changes, including new T-wave changes and ST-segment depressions, occurred in 64% of patients in the panobinostat-containing arm and 42% in the control arm. Arrhythmias occurred more frequently in patients receiving panobinostat compared to the control arm (12% vs. 5%).

Panobinostat will be approved with a BOXED WARNING alerting patients and health care providers of severe and fatal cardiac toxicities and severe diarrhea. Hemorrhage and hepatotoxicity are other important safety concerns with panobinostat and are included in the WARNINGS and PRECAUTIONS section of the label.

8. Advisory Committee Meeting

This application was presented to the ODAC on November 6, 2014. ODAC members voted on the following question: "Given this benefit:risk profile of the addition of panobinostat to bortezomib and dexamethasone, does the benefit outweigh the risks for patients with relapsed MM?"

Voting Result: Yes: 2 No: 5 Abstain: 0

Committee Discussion: The majority of the Committee voted "no" with many describing unease with the lack of additional data, such as improvement in OS or quality of life endpoints, to support the observed improvement in PFS. While these Committee members generally agreed that Trial 2308 demonstrated panobinostat activity in patients with myeloma, concerns with the toxicity and uncertain magnitude of PFS improvement were cited as contributing to a negative benefit:risk profile overall. Some members hypothesized that toxicities exhibited on Trial 2308 may be better managed in the United States as compared to the international sites from the trial; however, the data under consideration does not provide evidence of this. One Committee member specifically questioned whether the dose and combination of agents from the trial was ideal for maximizing benefit while minimizing toxicity. With regard to magnitude of improvement in PFS, some Committee members referred to the censoring and missing data as raising questions about this magnitude.

Those Committee members who voted "yes" discussed that magnitude of improvement in PFS was sufficient to support a positive benefit:risk profile for the use of panobinostat in this patient population.

9. Pediatrics

Panobinostat was granted orphan drug designation for this indication on August 20, 2012, and is exempt from PREA requirements.

10. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Accelerated Approval.

- Risk Benefit Assessment

The applicant proposed that panobinostat should be used in all patients with relapsed MM, but the benefit-risk assessment does not support approval for that indication.

In a pre-specified subgroup analysis of patients who had received prior treatment with both bortezomib and an immunomodulatory agent and a median number of two prior treatments, there is a favorable benefit-risk assessment for accelerated approval. Accelerated approval is based on the finding of prolonged PFS and an acceptable safety profile in a subgroup population of patients from Trial D2308. Verification of clinical benefit is required.

There are no available therapies for patients who have received at least two prior regimens that includes bortezomib and an immunomodulatory agent. This is an area of unmet medical need. Kyprolis and Pomalyst have third line indications, but they both remain under accelerated approval and not considered available therapies.

For the pre-specified subset that the review team agreed to grant an indication, the Hazard Ratio for PFS was 0.56 for a 4.8 month improvement in median PFS between arms for panobinostat. ORR was 55% on the panobinostat + BD arm with a median DOR of 12.0 months vs. 41% in the placebo + BD arm with median DOR of 8.3 months.

The safety profile for panobinostat appears acceptable for a more heavily pretreated population of patients with MM than the Applicant originally proposed, as long as the risks are adequately communicated in labeling and through a Risk Evaluation and Mitigation Strategy. The risks that are recommended for enhanced communication are severe diarrhea and cardiac toxicities (ischemia, arrhythmias, and ECG changes).

In agreement with the ODAC recommendation, the Agency is not approving FARYDAK for the broad indication for panobinostat for the treatment of all patients with relapsed MM, requested by the Applicant. However, in agreement with views expressed at the ODAC meeting, the Agency is granting accelerated approval for a more refractory population of patients with MM, those who have received at least 2 prior treatment regimens, who may have fewer available treatment options, and who appear to benefit in terms of prolongation of PFS. The risk-benefit profile was assessed by Drs. Kaminskas, Kwitkowski, George, Verdun and Miller. I recommend approval of this application.

- Recommendation for Postmarketing Risk Management Activities
REMS is required to mitigate risks of severe diarrhea and cardiac toxicities.
- Recommendation for other Postmarketing Study Commitments
See action letter.

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

/s/

TAMY E KIM
02/23/2015

RICHARD PAZDUR
02/23/2015