CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205353Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Edvardas Kaminskas, M.D.
Subject	Deputy Division Director Summary Review
NDA # **Supplement #**	205353
Applicant Name	Novartis Pharmaceuticals Corporation
Date of Submission	March 24, 2014
PDUFA Goal Date	November 24, 2014 (Major Amendment on 11/21/14 extended to 02/24/15)
Proprietary Name / **Established (USAN) 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
Recommended Action:	*Accelerated Approval with the following indication:* FARYDAK, a histone deacetylase inhibitor, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent.

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Barry W. Miller, M.S.N., C.R.N.P./Adam George, Pharm.D./Nicole Gormley, M.D., Ph.D./Virginia E. Kwitkowski, M.S., R.N., ACNP-BC.
Statistical Review	Chia-Wen Ko, Ph.D./Lei Nie, Ph.D./Rajeshwari Sridhara, Ph.D.
Pharmacology Toxicology Review	Emily Place, Ph.D., M.P.H./Kimberly Ringgold, Ph.D./Haleh Saber, Ph.D./John K. Leighton, Ph.D.
CMC Review/Biopharmaceutics Review/Product Quality Microbiology Review	Danuta Gromek-Woods, Ph.D./Ali H. Al Hakim, Ph.D./Elsbeth G. Chikhale, Ph.D./Angelica Dorantes, Ph.D./Erica Pfeiler, Ph.D.
Clinical Pharmacology and Pharmacometrics Review	Joseph Grillo, Pharm.D./Sarah Dorff, Ph.D./Bahru Habtemariam, Pharm.D./Lian Ma, Ph.D./Nitin Mehrota, Ph.D./Ping Zhao, Ph.D.
OSE/DMPP	Nathan Caulk, M.S., R.N., B.S.N./Barbara Fuller, R.N., M.S.N.

OPDP	Adam N. George, Pharm.D.
OSI/DGCPC	Anthony Orencia, M.D./Janice Pohlman, M.D., M.P.H./Kassa Ayalew, M.D., M.P.H.
CDTL Review	Virginia Kwitkowski, M.S., R.N., ACNP-BC.
OSE/OMEPRM/DMEPA	Michelle Rutledge, Pharm.D./Yelena Maslov, Pharm.D./Todd Bridges, Pharm. D.
OSE/OMEPRM/DRISK	Suzanne Robottom, Pharm. D./Doris Auth, Pharm. D./Cynthia LaCivita, Pharm.D.

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=Divisiion of Risk Management
OSI=Office of Scientific Investigations
DGCPC=Division of Good Clinical Practice Compliance
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

NDA 205353 is for pabinostat (LBH589, FARYDAK®), a histone deacetylase inhibitor, which has been extensively studied and continues to be studied by the Sponsor in a variety of oncologic diseases either as a single agent or in a variety of combinations with approved drugs. ClinicalTrials.gov lists 121 clinical trials that have been completed, remain active, or are currently enrolling study subjects. Pabinostat has not been approved for any indication either in the U.S. or in any other country. Initial IND (67091) was submitted to the FDA on 03/14/2003 for the intravenous formulation of LBH589. Initial IND (69862) for the oral formulation was submitted on 05/17/2004. On 11/03/2006 the Sponsor submitted a study protocol for a single arm trial entitled "Phase II study of LBH589 in adult patients with multiple myeloma who have received at least two prior lines of therapy and whose disease is refractory to the most recent line of therapy". The Agency recommended that the Sponsor conduct a randomized trial, rather than proceeding with the single-arm trial for accelerated approval.

The Sponsor and the Agency had a Type C meeting on 02/29/2012 to discuss the statistical and clinical issues related to trial CLBH589D2308 [a Phase III, randomized, double-blind, placebo-controlled study in 768 patients with relapsed multiple myeloma to assess the efficacy and safety of panobinostat in combination with bortezomib and dexamethasone (n=387) compared with placebo in combination with bortezomib and dexamethasone (n=381)], which is the principal trial submitted in this NDA. The Sponsor proposed to use the first interim analysis for safety and to move the second interim analysis to the time when approximately

368 events (80% information) had occurred. The Sponsor and the Agency had a Type B meeting on 02/05/2014 to discuss the content and the format of the NDA. The proposed indication is "Panobinostat in combination with bortezomib and dexamethasone is indicated for the treatment of patients with multiple myeloma, who have received at least 1 prior therapy".

2. Background

Drugs approved for the treatment of multiple myeloma include cyclophosphamide (1959), melphalan (1964), carmustine (1977), Velcade (bortezomib) (2003), Revlimid (lenalidomide) with dexamethasone (2006), Thalomid (thalidomide) with dexamethasone (2006), Doxil (liposomal doxorubicin) with bortezomib (2007), Kyprolis (carfilzomib) (2012), and Pomalyst (pomalidomide) (2013). Velcade, Revlimid, Doxil, Kyprolis, and Pomalyst are specifically approved in indications as second- or third-line treatments in relapsed or refractory patients. Dexamethasone is not specifically approved for treatment of multiple myeloma, but is often used in combinations resulting in enhanced therapeutic effects. Increasingly patients are being treated with 2-drug or 3-drug combinations in first-line as well as in relapsed/ refractory settings. Thus, the design of the pabinostat trial that is submitted in this NDA is appropriate and similar to trials of other multiple myeloma drugs.

The main issues in this NDA are the uncertainty of efficacy findings due missing data and consequent censoring, and the toxicity of panobinostat used in combination with bortezomib and dexamethasone, leading to uncertainty of benefit as related to risk.

3. CMC/Device

The Active Pharmaceutical Ingredient of the FARYDAK® hard gelatin capsules is panobinostat lactate anhydrous. Panobinostat lactate anhydrous is slightly soluble in water; solubility is pH-dependent, with the highest solubility in citrate buffer (pH 3.0). The dissolution acceptance criterion of Q= (b) (4)% at 15 minutes for Panobinostat Capsules is found acceptable. Based on drug product stability data, the expiration period for the Pabinostat capsules is 36 months.

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Overall, NDA 205353 is recommended for "Approval" from the CMC perspective.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

Pabionostat is a histone deacetylase inhibitor with activity to HDAC isoforms in class I, II, and IV at low nanomolar concentrations *in vitro*. Pabinostat promoted the accumulation of acetylated histones and non-histone proteins in cells. Pabinostat promoted cell death and cell cycle arrest *in vitro*, including human multiple myeloma cells. Pabinostat also promoted cell death in multiple myeloma cells from patients *ex vivo* and in both xenograft and disseminated mouse models of myeloma. Tumor tissues dissected from mice xenografts that were treated with pabinostat showed increased levels of acetylated histones. Pabinostat in combination with bortezomib and dexamethasone had higher activity in reducing tumor burden and increasing survival compared to controls.

Animal toxicology studies were conducted in appropriate species, using the administration route and dosing regimens that adequately addressed safety concerns in humans. Pabinostat-related toxicities in rats and/or dogs included the 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. Pabinostat 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 telemetered dogs.

Pabinostat 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.

Pharmacology/Toxicology review team concluded that no additional nonclinical studies are needed to support approval of FARYDAK for the proposed indication and that from a nonclinical perspective FARYDAK may be approved.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The clinical Pharmacology/Biopharmaceutics review team in their review concluded that

- The proposed treatment regimen is not supported by the totality of evidence based on efficacy and safety from the Phase 1b dose escalation trial and the registration trial. The results of both studies show the absence of acceptable therapeutic window for the overall clinical benefit at the proposed dose. Specifically, 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

pabinostat 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 thus may offer 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 $AUC_{0\text{-}inf}$ 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) increase the C_{max} and $AUC_{0\text{-}48}$ 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.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics review team that there are no outstanding clinical pharmacology issues that would preclude approval with two PMRs.

6. Clinical Microbiology

N/A. Panobinostat is an oral anti-cancer agent.

7. Clinical/Statistical-Efficacy

Efficacy and safety of pabinostat was evaluated in one randomized trial (LBH589D2308, abbreviated as D2308) and two single-arm trials (a Phase 1b dose finding study of pabinostat and bortezomib in patients with multiple myeloma and a Phase 2 single-arm trial of pabinostat and bortezomib and dexamethasone in 55 patients with relapsed and bortezomib-refractory multiple myeloma).

Trial D2308 was a large, international, randomized (1:1), double-blinded, placebo-controlled trial in which 768 subjects with relapsed multiple myeloma 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) based on modified European Bone Marrow Transplant Group (EBMT) criteria. The key secondary endpoint was overall survival (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 pabinostat + 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 1 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’.

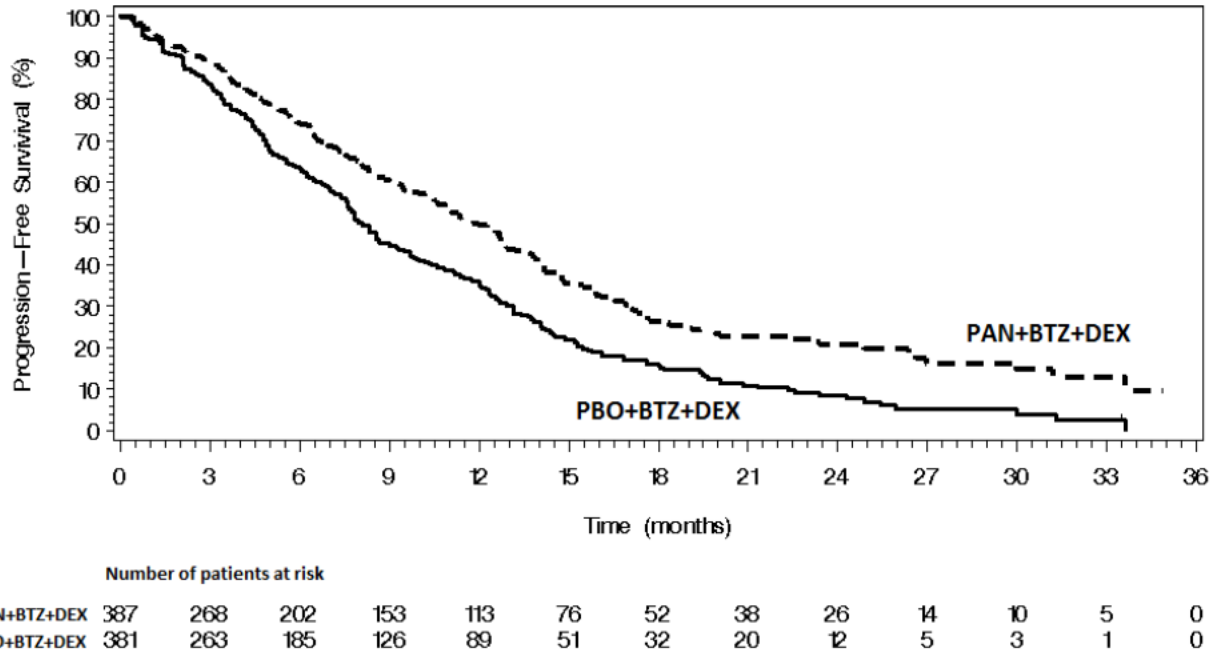
Table 1 Progression-free Survival by Investigator

	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
[1] Kaplan-Meier estimates
[Source: FDA analysis]

Figure 1 shows the Kaplan-Meier plot of PFS by Investigator.

Figure 1 Kaplan-Meier estimates of Progression Free Survival in Trial 2308



As noted in Table 1, 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 Independent Review Committee showed a median PFS of 9.9 months in the pabinostat + 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 Overall Survival 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 Overall Survival, 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 (see below). Oncology Drugs Advisory Committee also did not feel that patients in the overall ITT population had a positive benefit/risk assessment for pabinostat 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 pabinostat + BD arm and 38% in the placebo + BD arm being 65 years or older, and a similar percentages in regard to race and gender as the ITT population. The median number of prior treatments was 2. The immunomodulatory agent most used was thalidomide.

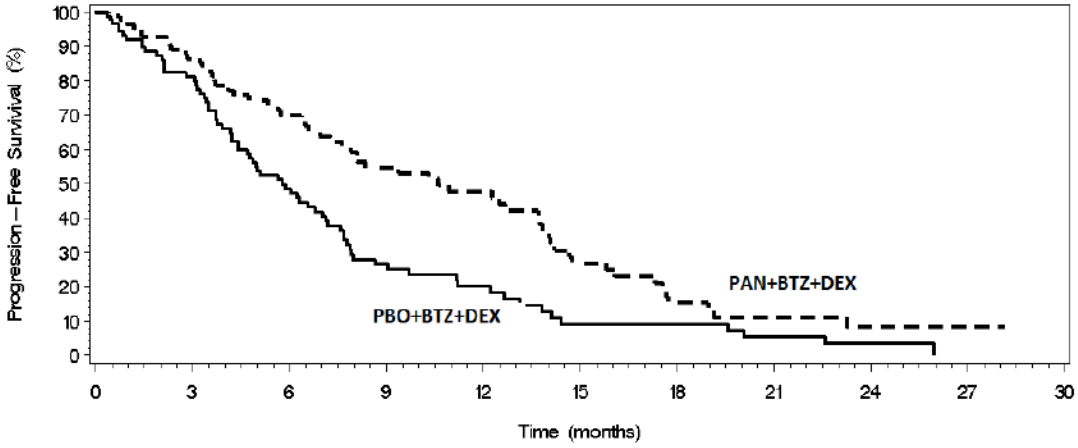
The key efficacy findings for this subset of patients are shown in Tables 2 and 3 and Figure 2. The difference in median PFS was 4.8 months, favoring the panobinostat + BD arm. This result is consistent with the statistically significant difference between arms in the overall population. There is a reduction 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 pabinostat + BD arm.

Table 2 Investigator-assessed Progression-free Survival (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 Progression-free Survival (PFS) from Trial D2308 subgroup: prior bortezomib and an immunomodulatory agent



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 3. The median duration of response was greater in the pabinostat + BD arm than in the placebo + BD arm, as it was in the overall population.

Table 3 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

Additional Supportive Trials

Phase 2 Trial
The supportive, single-arm trial CLBH589DUS71 enrolled 55 patients with relapsed and bortezomib-refractory multiple myeloma. All received panobinostat, bortezomib, and dexamethasone as given in the randomized trial. This trial enrolled U.S. patients with a median age of 61 years (range 41-88); 62% were less than 65 years of age, and 53% were male. Most patients (92%) were considered ECOG performance status 0 or 1. All patients had received bortezomib and were considered refractory to it as defined by progressive disease within 60 days of the last bortezomib-containing therapy. At the end of 8 cycles, the ORR was 34.5% with a median DOR of 6 months. No patients achieved a Complete Response.

Phase 1b dose-escalation trial
Trial LBH589B2207 enrolled 47 patients who had received at least one prior therapy for MM. Based on the results of adaptive Bayesian logistic model integrated with information from clinical assessment of the toxicity profiles observed, the dose of panobinostat 20 mg + bortezomib 1.3 mg/m^2 was considered as MTD. In the 3 times weekly, two weeks on/one week off schedule, panobinostat 20 mg + bortezomib 1.3 mg/m^2 + dexamethasone 20 mg was considered as the recommended dose.

8. Safety

The total number of subjects who were treated with pabinostat at the recommended dose and schedule the pabiostat + bortezomib + dexamethasone was 456 (386 in Trial D2308, 15 in the expansion cohort of Trial B2207, and 55 in Trial DUS71); however, the main analyses focused

on the randomized trial with the placebo + bortezomib + dexamethasone arm. The adverse event profile of the supportive trials was consistent with that of the randomized trial. The key findings may be summarized as follows (from the Safety Review):

Based upon review of the safety data from 758 patients with relapsed multiple myeloma evaluable for safety in the randomized, double-blind, placebo controlled trial (D2308), the regimen of panobinostat 20 mg administered orally once daily 3 times a week (days 1, 3, 5, 8, 10, 12), on a 2 weeks on 1 week off schedule for up to 16 cycles in combination with bortezomib and dexamethasone is associated with added toxicity and is not well tolerated compared to treatment with bortezomib and dexamethasone. In trial D2308 there were 386 patients who were exposed to investigational therapy with panobinostat 20 mg in combination with bortezomib and dexamethasone. A total of 372 patients were exposed to the control arm of bortezomib in combination with dexamethasone (a standard U.S. regimen for the treatment of relapsed multiple myeloma).

Grade 1-4 adverse events occurred in 99.7% of patients in both treatment arms. The most common adverse events that occurred in ≥20% of patients in the panobinostat arm and at a ≥10% greater frequency than in the control arm were diarrhea, thrombocytopenia, fatigue, nausea, neutropenia, peripheral edema, decreased appetite, hypokalemia, pyrexia and vomiting.

The frequency of patients that experienced grade ≥3 adverse events was higher in the panobinostat arm 95% (n=367) compared to the incidence in the control arm 83% (n=307). The most common (>10%) grade ≥3 toxicities that occurred more frequently in the panobinostat arm compared to the control arm were thrombocytopenia (67% vs. 31%), diarrhea (25% vs. 8%), fatigue/asthenia (25% vs. 12%), pneumonia (10% vs. 8%), neutropenia (34% vs. 11%), hypophosphatemia (20% vs. 12%), hypokalemia (18% vs. 7%), and hyponatremia (13% vs. 7%).

Serious adverse events (SAEs) were also more common in the panobinostat arm with 230 patients (60%) experiencing at least 1 SAE compared to 155 patients (42%) in the control arm. The most common SAEs that occurred in ≥5% of patients in the panobinostat arm compared to the control arm were pneumonia (18% vs. 11%), diarrhea (11% vs. 2%), thrombocytopenia (7% vs. 2%) fatigue (6% vs. 2%), and sepsis (6% vs. 2%). Fifty-five percent (55%) of patients treated with panobinostat (n=211) experienced an adverse event that led to hospitalization or prolongation of hospitalization compared to 37% (n=138) of patients treated with the control arm.

The addition of panobinostat to bortezomib and dexamethasone led to reduced tolerability. Overall, 36% of patients receiving panobinostat discontinued therapy due to an adverse event compared to 20% of patients (n=76) in the control arm. The most common reason for treatment discontinuation in the panobinostat arm was diarrhea which accounted for 4% of patients in the panobinostat arm compared to 2% of patients in the control arm. Adverse events of any toxicity grade leading to treatment interruption or dose modification occurred 89% of patients in the panobinostat arm

compared to 76% patients in the control arm. The two most common reasons for dose modification or treatment interruption in the panobinostat arm compared to the control arm were thrombocytopenia and diarrhea.

During the trial, 26 patients (7%) in the panobinostat arm died due to treatment-emergent toxicities compared to 12 patients (3%) in the control arm. (Deaths due to disease progression occurred in 4 and 6 patients in the pabinostat and control arms, respectively). The categories of hemorrhage and infection were the main contributors to the observed imbalance of deaths between the treatment arms. Five patients in the panobinostat arm died due to hemorrhage compared to 1 patient in the control arm, and 10 patients died due to infection in the panobinostat arm compared to 6 in the control arm. Deaths due to cardiac disorders occurred in 4 and 3 patients, respectively.

The toxicities of primary concern with this application were asthenic conditions (asthenia, fatigue, lethargy, malaise), severe gastrointestinal toxicity (nausea, vomiting and diarrhea) leading to serious events of dehydration, severe thrombocytopenia leading to serious hemorrhagic events, neutropenia resulting in severe infections such as pneumonia and sepsis.

Of particular concern is the increased number of deaths due to hemorrhage. All 5 of the patients who died due to hemorrhage had grade >3 thrombocytopenia at the time of the event. Patients in the control arm of trial D2308 also experienced grade ≥3 events of thrombocytopenia but in contrast only 1 patient died.

This finding implies that the dose modification and supportive care strategies used to mitigate the risk of hemorrhage due to thrombocytopenia with panobinostat were not adequate. This is particularly concerning given the fact that in clinical practice patients may not be monitored as frequently and may therefore be subjected to an increased risk of bleeding due to severe thrombocytopenia.

Submission Specific Primary Safety Concerns with Panobinostat

Gastrointestinal Toxicity-
Of the gastrointestinal toxicities, diarrhea had the largest impact on the tolerability of panobinostat, as described above, leading to treatment interruption, dose modification and treatment discontinuation. During the trial 173 (45%) patients in the panobinostat arm compared to 96 (26%) required antipropulsives (e.g., Lomotil or Immodium).

Cytopenias-
Thrombocytopenia: Severe thrombocytopenia is of clinical concern as it because it increases the risk of bleeding and may require platelet transfusion. Thirty percent (30%) of patients in the panobinostat arm required a platelet transfusion due to thrombocytopenia compared to 10% of patients in the placebo arm. Additionally, 31% of patients in the panobinostat arm required dose modification/interruption due to thrombocytopenia compared to 11% of patients in the placebo arm. The rate of hemorrhagic events of all toxicity grades 1-4 was 8% greater in the panobinostat arm compared to the placebo arm. There was also a two fold increase in severe

(grade 3-4) and serious events of hemorrhage in the panobinostat arm compared to the placebo arm.
Neutropenia: Neutropenia that required dose interruption or modification occurred in 10% of patients in the panobinostat arm compared to 2% of patients in the placebo arm. Consistent with the increased rate of severe neutropenia, colony stimulating factor (GCSF or GMCSF) use was higher in the panobinostat arm than the placebo arm (13% vs. 4%).

Cardiac Toxicity-
Ischemia: Cardiac ischemic events are uncommon but serious adverse events associated with the pharmacologic class of HDAC inhibitors and also of bortezomib. In trial D2308, three patients in the panobinostat arm died due to cardiac ischemia and none in the placebo arm. All grade ischemic events were increased by 3% by the addition of panobinostat to bortezomib and dexamethasone in trial D2308.

ECG Changes: Treatment-emergent ECG changes occurred in 64% of patients in the panobinostat arm compared with 42% in the placebo arm. The incidence of QT-prolongation was similar between treatment arms, 12% in the panobinostat arm, and 8% in the placebo arm. New T-wave changes were reported in 40% of patients in the panobinostat arm compared with 18% in the placebo arm. ST-segment depressions were reported in 22% of patients in the panobinostat arm, compared with 4% in the placebo arm.

Asthenic conditions- The addition of panobinostat to bortezomib and dexamethasone in Trial D2308 produced a 12% increase in the all grade asthenic conditions and an 11% increase in the grade ≥3. Asthenic conditions lead to treatment discontinuation in 6% of patients in the panobinostat arm compared with 3% in the placebo arm.

9. Advisory Committee Meeting

This application was presented to the Oncologic Drugs Advisory Committee on November 6, 2014. Following the presentations by the FDA and the Applicant, the following question was posed to the Committee:

1. **VOTE:** Given this benefit:risk profile of the addition of panobinostat to bortezomib and dexamethasone, does the benefit outweigh the risks for patients with relapsed multiple myeloma?

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

   Committee Discussion: The majority of the Committee voted "no." Those Committee members who voted in the negative described unease regarding the lack of additional data, such as improvement in overall survival or quality of life endpoints, to support the observed improvement in progression-free survival (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. Several Committee members who voted "no" encouraged the Applicant to continue to pursue clinical development of this agent in hopes of better elucidating a population of patients with multiple myeloma who would safely benefit from treatment with panobinostat in combination with other treatment.

Those Committee members who voted "yes" described a judgment that the demonstrated magnitude of improvement in PFS was sufficient to support a positive benefit:risk profile for the use of panobinostat in this complex and challenging population of patients.

10. Pediatrics

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

11. Other Relevant Regulatory Issues

Consults:

OSE/DRISK: Assisted in the formulation of risk management approach.
OSI: A single domestic and a single foreign clinical study site were selected for audit on the basis of being the largest enrolling sites. The domestic site was given a NAI classification, indicating, there were no deviations from regulations and the data is acceptable. The foreign site was given a VAI classification, indicating there were deviations from regulations, but the data is acceptable.

There are no other unresolved relevant regulatory issues.

12. Labeling

Proprietary name: FARYDAK

Indication: FARYDAK, a histone deacetylase inhibitor, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with multiple myeloma who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Boxed warning: Fatal and Serious Toxicities: Severe Diarrhea and Cardiac Toxicities

The Agency and the Applicant resolved all differences regarding labeling.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Accelerated Approval for the indication as stated in 12. Labeling and Post-marketing Commitments as described below.

- Risk Benefit Assessment

In agreement with the ODAC recommendation, the Agency is not approving FARYDAK for the broad indication requested by the Applicant. However, again in agreement with views expressed at the ODAC meeting, the Agency is granting accelerated approval for a more refractory population of patients with multiple myeloma, 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 progression-free survival. FARYDAK is a HDAC inhibitor, a new class of drugs for treatment of patients with multiple myeloma. A detailed Risk Benefit Assessment is presented in the CDTL review.

- Recommendation for Postmarketing Risk Management Activities
  REMS in process of being formulated.

- Recommendation for other Postmarketing Study Commitments

- ***PMR 2181 -1: Conduct a randomized phase 2 clinical trial of panobinostat in combination with subcutaneous bortezomib and dexamethasone to characterize the safety and efficacy of at least two different doses of panobinostat. Eligible patients will include patients with relapsed multiple myeloma who have been previously exposed to immunomodulatory agents. The primary objective is to assess the overall response rate (ORR) in all treatment arms according to International Myeloma Working Group (IMWG) criteria by investigator assessment. The study should include one interim analysis. The results of this trial will be used to inform the dose selection for the confirmatory Phase 3 trial. Submit a final study report with full datasets.***

- Preliminary Protocol Submission to Include SAP: April 2015

- Final Protocol Submission: September 2015
- Interim Analysis: August 2017
- Trial Completion: August 2018
- Final Report Submission: August 2019

- ***PMR 2181--2: Conduct a multicenter, randomized, placebo-controlled phase 3 trial comparing panobinostat in combination with subcutaneous bortezomib and dexamethasone with subcutaneous bortezomib and dexamethasone in patients with relapsed multiple myeloma who have been previously exposed to immunomodulatory agents. The panobinostat dose selection will be based upon the interim analysis of the trial described in PMR 2181-1. Eligible patients will have previously treated multiple myeloma, 1-3 prior lines of therapy, prior immunomodulatory agent exposure (either thalidomide, lenalidomide, or pomalidomide), and measurable disease. The primary objective is to compare the progression free survival (PFS) in both treatment arms by investigator assessment.***

- Preliminary Protocol Submission to Include SAP: March 2017
- Final Protocol Submission: November 2017
- Trial Completion: February 2021
- Final Report Submission: December 2021

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/s/

EDVARDAS KAMINSKAS
02/20/2015