FARYDAK®

Panobinostat (as lactate)

WARNING

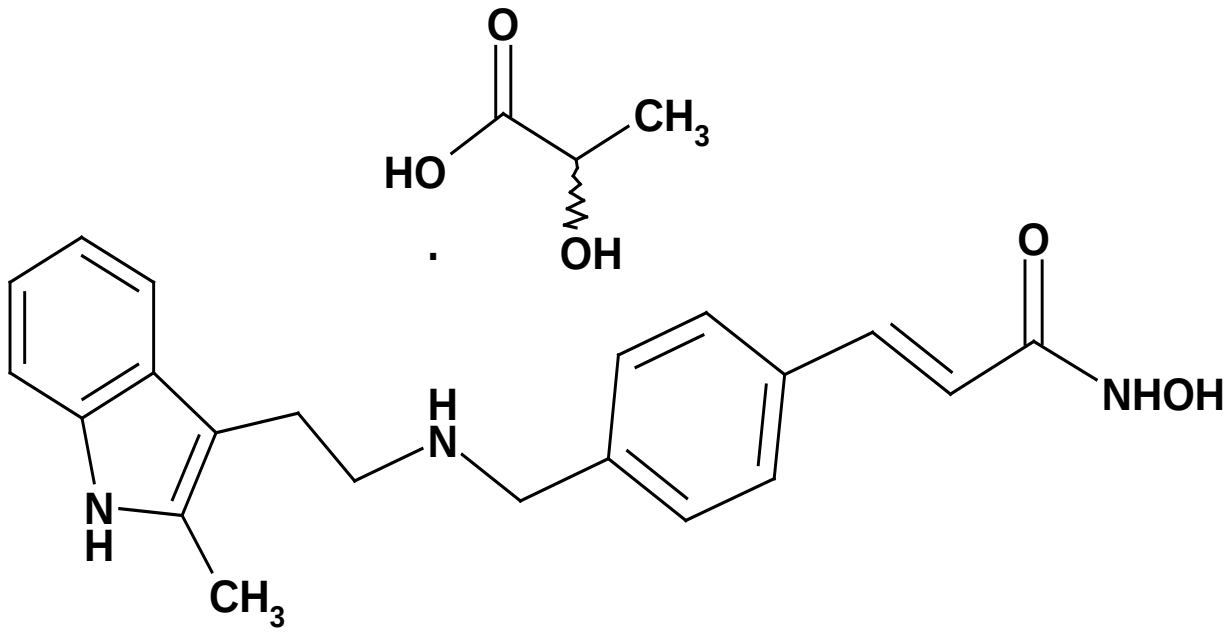
Diarrhoea occurred in 68% of FARYDAK-treated patients, was severe in 25%, resulting in dehydration and electrolyte disturbances. Monitor patients carefully particularly in those with pre-existing renal failure. Two fatalities resulting from acute renal failure were reported in FARYDAK treated patients.

Severe and fatal cardiac ischaemic events, severe arrhythmias, and ECG changes have occurred in patients receiving FARYDAK. Arrhythmias may be exacerbated by electrolyte abnormalities.

Severe neutropenia occurred in 34% of FARYDAK treated patients and may contribute to an increased risk of serious and fatal infections.

Severe thrombocytopenia occurred in 67% of FARYDAK treated patients and may be associated with an increased risk of serious and fatal haemorrhage.

Close monitoring of patients is required (see Precautions; Dosage and Administration section for monitoring recommendations and dose modifications).



Panobinostat (free base): $C_{21}H_{23}N_3O_2$; CAS: 404950-80-7

Panobinostat lactate (salt form on anhydrous basis): $C_{21}H_{23}N_3O_2.C_3H_6O_3$; CAS: 960055-56-5

Relative molecular mass: 349.4 (free base) + 90.1 (lactic acid) = 439.5

Description

Panobinostat (as lactate) is a white to slightly yellowish or brownish powder that is slightly soluble in water, ethanol (25°C) and practically insoluble in n-octanol. The pH of a 0.1% (m/V) aqueous solution of panobinostat lactate, anhydrous at room temperature (21-22°C), measured potentiometrically is approximately 6.0.

The capsule active contents are:

FARYDAK 10 mg hard capsule contains 10 mg panobinostat (12.576 mg panobinostat lactate), FARYDAK 15 mg hard capsule contains 15 mg panobinostat (18.864 mg panobinostat lactate) and FARYDAK 20 mg hard capsule contains 20 mg panobinostat (25.152 mg panobinostat lactate).

The capsule inactive contents are: Magnesium stearate, mannitol, microcrystalline cellulose, pregelatinised maize starch.

The hard capsule is made from gelatin and the capsule colouring agents are:

10 mg: titanium dioxide, brilliant blue FCF, iron oxide yellow.

15 mg: Titanium dioxide, iron oxide yellow, iron oxide red.

20 mg: Titanium dioxide and iron oxide red.

The printing ink is OPACODE monogramming ink S-1-17823 BLACK.

Pharmacology

Pharmacodynamics

Panobinostat, a hydroxamic acid derivative, is a class I/II/IV pan-deacetylase inhibitor (HDACi). HDACi are a novel class of anticancer agents that target epigenetic changes via gene expression modulation. Panobinostat inhibits the proliferation of a variety of tumour cell lines at low nanomolar concentrations and activates the p21 promoter, a key mediator of G1 arrest and differentiation *in vitro*. The parent drug is deemed to be responsible for the overall pharmacological activity of panobinostat. Treatment of tumour cells with panobinostat resulted in a dose dependent increase in acetylation of histones H3 and H4 at low nanomolar

concentrations. Under *in vitro* conditions, tumour cells were more sensitive to the cytotoxic effects of panobinostat than normal cells. Tumour tissues excised from mouse xenografts from *in vivo* efficacy studies exhibited inhibition of histone deacetylases and higher levels of histone acetylation, which correlated with decreased tumour burden.

Pharmacokinetics

Absorption

Panobinostat is rapidly absorbed with Tmax reached within 2 hours of oral administration in patients with advanced cancer. The absolute bioavailability of panobinostat has not been determined in a formal study however it is expected to be low (~21%). Panobinostat has linear pharmacokinetics over the dose range of 10 mg to 80 mg.

Overall panobinostat exposure and inter-patient variability remained unchanged with or without food. Plasma panobinostat Cmax and $AUC_{0–48}$ was 44% and 16% lower compared to fasting conditions, respectively, following ingestion of an oral FARYDAK dose 30 minutes after a high-fat meal by 36 patients with advanced cancer. Tmax was prolonged by 1.5 to 2.5 hours with food (i.e., both normal and high fat breakfasts). Since food did not alter overall bioavailability (AUC), panobinostat can be administered with food in cancer patients.

The aqueous solubility of panobinostat is pH dependent, with higher pH resulting in lower solubility. Co-administration of FARYDAK with drugs that elevate the gastric pH was not evaluated in vitro or in a clinical trial; however, altered panobinostat absorption was not observed in simulations using physiologically-based pharmacokinetic (PBPK) models.

Distribution

Panobinostat is moderately (approximately 90%) bound to human plasma proteins. Its fraction in the erythrocyte is 0.60 *in vitro*, independent of the concentration. Displacement of highly protein-bound compounds by panobinostat is unlikely.

Metabolism

Panobinostat is extensively metabolized. Pertinent metabolic pathways involved in the biotransformation of panobinostat are reduction, hydrolysis, oxidation, and glucuronidation processes. Oxidative metabolism of panobinostat played a less prominent role with approximately 40% of the dose eliminated by this pathway. Cytochrome P450 3A4 (CYP3A4) is the main oxidation enzyme with minor involvement of CYP2D6 and 2C19.

Panobinostat represented 6 to 9% of the drug related exposure in plasma.

Elimination

After a single oral dose of [^{14}C] panobinostat in patients, 29 to 51% of administered radioactivity is excreted in the urine and 44 to 77% in the faeces. Unchanged panobinostat accounted for <2.5% of the dose in urine and <3.5% of the dose in faeces. The remainders are metabolites. An oral clearance (CL/F) and terminal elimination half-life ($t_{1/2}$) of approximately 160 L/hr and 37 hours, respectively, was estimated based on the final parameter estimates from a population pharmacokinetic (pop-PK) model in patients with advanced cancer. An inter-subject variability 65% on the clearance estimate was also reported.. . Up to 2-fold accumulation was observed with chronic oral dosing in patients with advanced cancer.

Special populations

Pediatric patients

Panobinostat was not evaluated in patients under 18 years of age.

Elderly patients

In the Phase III clinical study 162 out of 387 patients were 65 or over. Plasma exposure of panobinostat in patients 65 years or younger was similar to those older than 65 years in the pooling of single-agent panobinostat studies between the dose range of 10 and 80 mg. Apparent panobinostat plasma clearance was 150.6 (70.3%) L/hr in 122 patients who are 65 years or younger and it was 171.0 (62.8%) L/hr in 86 patients who are older than 65.

Patients with hepatic impairment

The effect of hepatic impairment on the pharmacokinetics of panobinostat has been evaluated in a Phase I study in 24 cancer patients with varying degrees of hepatic impairment. In patients with NCI-CTEP class mild (i.e., Group B) and moderate (i.e., Group C) hepatic impairment, $AUC_{0\text{-inf}}$ increased 43% and 105% compared to the group with normal hepatic function, respectively. The relative change in C_{max} followed a similar pattern. The effect of severe hepatic impairment was indeterminate in this study due to the small sample size (n=1). A dose modification is recommended for patients with mild and moderate hepatic impairment (see Dosage and Administration and Precautions).

Patients with renal impairment

The effect of renal impairment on the pharmacokinetics of panobinostat was assessed in a Phase I study in 37 patients with advanced solid tumours with varying degrees of renal functions. Mild, moderate and severe renal impairment based on baseline urine creatinine clearance did not increase the panobinostat plasma exposure in mild, moderate and severe groups. Dose modification is not recommended when treating these patients with FARYDAK (see Dosage and Administration).

Attachment 1: Product information Farydak - Panobinostat lactate - Novartis Pharmaceuticals Australia Pty Ltd - PM-2014-03146-1-4 – FINAL - 22 October 2018. This Product information was approved at the time this AusPAR was published.

Clinical Trials

Introduction

Patients enrolled in the Phase III Study D2308 received 1 to 3 prior therapies according to the inclusion criteria. Registration has been granted for a heavily pre-treated subgroup (2), restricted further from a pre-specified subgroup (1) on the basis of unmet medical need. Subgroup 2 is a population of heavily pre-treated patients who have received at least 2 prior regimens including BTZ and an IMiD and includes 19% of the patients of the Study D2308 population and 76% of the patients from the pre-specified subgroup 1 population having prior treatment with bortezomib and an immunomodulatory agent. The median age of patients in Study D2308 was 63 years, ranging from 28-84 years. In subgroup 2 the median age was 61 years, ranging from 32-79 years with no patients over the age of 80 years.

Clinical efficacy in patients with relapsed and relapsed and refractory Multiple Myeloma (Study D2308)

The efficacy and safety of panobinostat in combination with bortezomib and dexamethasone was evaluated in a Phase III randomized, double-blind, placebo-controlled, multicenter study in patients with relapsed or relapsed-and-refractory multiple myeloma who had received 1-3 prior lines of therapies.

Patients received panobinostat (20 mg/day, taken orally once a day, three times per week, on a 2 weeks on 1 week off dosing regimen, in combination with bortezomib (1.3 mg/m^2 injected intravenously and dexamethasone (20 mg). Treatment was administered for a maximum of 16 cycles (see Table 4 and 5).

A total of 768 patients were randomized in a 1:1 ratio to panobinostat+ bortezomib + dexamethasone (n=387) or placebo + bortezomib + dexamethasone arm (n=381), stratified by prior use of bortezomib [Yes (n=336 (43.8%)), No (n=432 (56.3%)] and number of prior lines of anti-myeloma therapy [1 prior line (n=352 (45.8%)), 2 to 3 prior lines (n=416 (54.2%))]. Demographics and baseline disease characteristics were balanced and comparable between the study arms.

The median age was 63 years, range 28-84; 42.1% of patients were older than 65 years. A total of 53.0% of patients were male. Caucasians comprised 65.0% of the study population, Asians 30.2%, black 2.9%. The ECOG performance status was 0-1 in 93% of patients. The median number of prior therapies was 1 and 48% of patients received 2 or 3 prior lines of therapy. More than half (57.2%) of the patients had prior stem cell transplantation and 62.8% of the patients were relapsed after previous antineoplastic therapies (e.g. melphalan 79.6%, dexamethasone 81.1%, thalidomide 51.2%, cyclophosphamide 45.3%, bortezomib 43.0%, combined bortezomib,

dexamethasone 37.8%, and lenalidomide 20.4%). More than one third (35.8%) of the patients were relapsed and refractory to prior treatment.

The FAS median duration of follow-up was 28.75 months in the panobinostat + bortezomib + dexamethasone arm and 29.04 months in the placebo + bortezomib + dexamethasone arm.

Subgroup 2 patients had a median of 3 prior therapies and the median duration of treatment in was 4.5 months in the panobinostat + bortezomib + dexamethasone arm and 4.8 months in the placebo + bortezomib + dexamethasone arm.

The primary endpoint was progression-free survival (PFS) as per modified European Bone Marrow Transplant Group (EBMT) criteria and as assessed by the investigator.

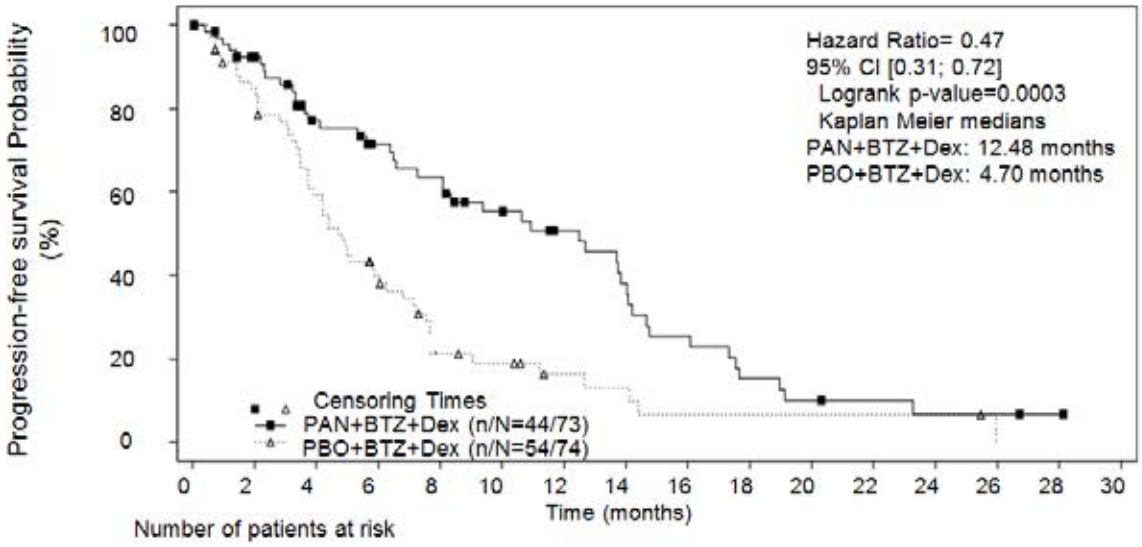
Subgroup 2 efficacy results are summarized in Table 1 and the Kaplan- Meier curves for PFS are provided in Figure 1. Since OS is not statistically significant in the overall population, results of OS analysis in subgroup 2 patients should be interpreted with caution. Deaths on treatment occurred in this subgroup (see BOXED WARNING page 1).

Table 1 Overview of efficacy data in patients who received at least two prior regimens including bortezomib and an immunomodulating agent (subgroup 2).

	FARYDAK **bortezomib and dexamethasone** **N= 73**	**PLACEBO** **bortezomib and dexamethasone** **N= 74**
Progression-free survival		
Median, months [95% CI]	12.5 [7.26, 14.03]	4.7 [3.71, 6.05]
Hazard ratio [95% CI][1]	0.47 (0.31, 0.72)	
Overall response[2]	43 (59%)	29 (39%)
[95% CI]	(46.8, 70.3)	(28, 51.2)
Complete response	6 (8%)	0
Near complete response	10 (14%)	6 (8%)
Partial response	27 (37%)	23 (31%)
Overall Survival		
Median, months [95% CI]	25.5 (95%CI: 19.6, 34.3)	19.5 (95%CI: 14.1, 32.5)

[1] Hazard ratio obtained from stratified Cox model; [2] Modified EBMT criteria

Figure 1 Kaplan-Meier plot of progression-free survival in patients with multiple myeloma who received at least two prior regimens including bortezomib and an immunomodulatory agent (subgroup 2)



Number of patients at risk

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
PAN+BTZ+Dex	73	57	42	36	32	25	20	15	10	6	4	3	2	2	1	0
PBO+BTZ+Dex	74	54	37	23	11	9	5	4	2	2	2	2	2	0	0	0

PAN= panobinostat, PBO= placebo, BTZ= bortezomib, Dex = dexamethasone

Indication

FARYDAK, in combination with bortezomib and dexamethasone, is indicated for the treatment of adult patients with relapsed and/or refractory multiple myeloma, who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent.

Treatment should be initiated and monitored by a specialist with experience in treating haematological malignancies.

Contraindications

Hypersensitivity to panobinostat or any other ingredients contained in FARYDAK.

Precautions

FARYDAK is used in combination treatment, therefore the prescribing information of bortezomib and dexamethasone should be consulted prior to initiation of treatment with FARYDAK.

Gastrointestinal disorders

Severe nausea, diarrhoea, constipation, and vomiting, sometimes requiring the use of anti-emetic and anti-diarrhoeal medications have been reported in patients treated with FARYDAK (see Adverse Effects). Diarrhoea was the most frequently reported AE in both clinical trial arms. Severe diarrhoea occurred in 25% of patients treated with FARYDAK compared to 8% of patients in the control arm (see Boxed Warning; Adverse Effects). Diarrhoea of any grade occurred in 68% of patients treated with FARYDAK compared to 42% of patients in the control arm. Diarrhoea can occur at any time. Treatment discontinuation was reported in a relatively small proportion of patients with diarrhoea at 4.5%, nausea and vomiting at 0.5% each.

Fluid and electrolyte blood levels, especially potassium, magnesium and phosphate, should be monitored periodically during therapy and corrected as clinically indicated to prevent potential dehydration and electrolyte disturbances (see Boxed Warning; Dosage and Administration).

Prophylactic anti-emetics should be administered at the discretion of the physician and in accordance with local medical practice. Anti-emetic drugs with a known QT prolongation risk, such as dolasetron, ondansetron and tropisetron should be used with caution (see Interactions with other Medicines).

Patients should be advised to contact their physicians when severe GI toxicity occurs. At the first sign of abdominal cramping, loose stools, or onset of diarrhoea, it is recommended that the patient be treated with anti-diarrhoeal medication or any additional treatment in accordance with local treatment guidelines. Replacement i.v. fluids and electrolytes may be used as appropriate. Drugs with laxative properties should be used with caution because of the potential for exacerbation of diarrhoea. Patients should be advised to contact their physician to discuss any laxative use (see Dosage and Administration).

Cardiac Toxicities

Severe and fatal cardiac ischemic events, as well as severe arrhythmias, and electrocardiogram (ECG) changes occurred in patients receiving FARYDAK (see Boxed Warning). In the Phase III clinical study, arrhythmias occurred in 12.1% of patients receiving PAN+BTZ+Dex, compared to 4.8% of patients in the PBO+BTZ+Dex arm. Cardiac ischemic events occurred in 3.7% of patients treated with FARYDAK compared with 1.3% of patients in the control arm.

Panobinostat may prolong cardiac ventricular repolarization (QT interval). In vitro electrophysiology data and in vivo telemetry studies in dogs showed consistent signals for QT prolongation.

QTc prolongation was observed, mostly mild in degree: QTcF interval > 450 ms and ≤ 480 ms was reported in 10.8% with maximum increase from baseline > 30 ms and ≤ 60 ms in 14.5% patient. No episodes of QTcF prolongation >500 msec have been reported with the dose of 20 mg FARYDAK in the Phase III clinical study, in combination with bortezomib and dexamethasone. Pooled clinical data from over 500 patients treated with single agent panobinostat in multiple indications and at different dose levels has shown that the incidence of CTCAE grade 3 QTc prolongation (QTcF >500 msec) was approximately 1% overall and 5% or more at a dose of 60 mg or higher. No episodes of Torsades de pointes have been observed in the oral panobinostat studies, but one case has been reported in an IV study.

Additional analysis suggests that the risk of QTc prolongation does not increase over time.

The percentage of patients with newly occurring qualitative ECG abnormalities in the phase III Study was higher in the PAN+BTZ+Dex treatment arm (63.5%) than in the PBO+BTZ+Dex arm (42.2%).

Changes in T wave and depressed ST segment were generally not associated with clinical symptoms and their clinical significance is therefore unknown.

T-wave changes: There were 39.6% of patients in the PAN+BTZ+Dex arm who reported newly occurring T wave changes vs. 18.3% in the PBO+BTZ+Dex arm in the phase III Study,.

ST-segment depression: In the phase III Study, ST-T segment changes were reported in 21.8% of patients in the PAN+BTZ+Dex arm and 3.4% in the PBO+BTZ+Dex arm, primarily involving ST-T depression (21.7% and 3.6%, respectively).

Tachyarrhythmias: In the phase III Study, the total number of patients with at least one event of tachyarrhythmia (ie atrial fibrillation, palpitations, sinus tachycardia, tachycardia) was 46 (12.1%) in the PAN+BTZ+Dex arm with 1.8% of grade 3/4 and 18 (4.8%) in the PBO+BTZ+Dex arm with 1.1% of grade 3/4.

Sinus tachycardia: Sinus tachycardia was commonly observed ECG finding, with 15.5% in the PAN+BTZ+Dex arm and 6.8% in the PBO+BTZ+Dex arm in the phase III Study.

Appropriate monitoring of serum electrolytes (e.g. potassium, magnesium, phosphorous) and ECG should be performed at baseline and periodically during treatment particularly in patients with severe gastrointestinal side effects (see section 4 Dosage and administration).

Do not initiate treatment with FARYDAK in patients with a QTcF ≥450 msec or clinically significant baseline ST-segment or T-wave abnormalities. Arrhythmias may be exacerbated by electrolyte abnormalities. If during treatment with FARYDAK the QTcF increases to ≥480 msec, interrupt treatment. Correct any electrolyte abnormalities. If QT prolongation does not resolve, discontinue treatment with FARYDAK.

Do not initiate treatment FARYDAK treatment in patients with history of recent myocardial infarction or unstable angina.

FARYDAK should be used with caution in patients who already have or who are at significant risk of developing QTc prolongation. This includes patients:

- With long QT syndrome.
- With uncontrolled or significant cardiac disease including congestive heart failure and clinically significant bradycardia.

Concomitant administration of medications that are known to cause QTc prolongation is not recommended (see Interactions).

Myelosuppression
FARYDAK causes myelosuppression, including severe thrombocytopenia, neutropenia and anaemia (CTCAE grade 3 to 4).

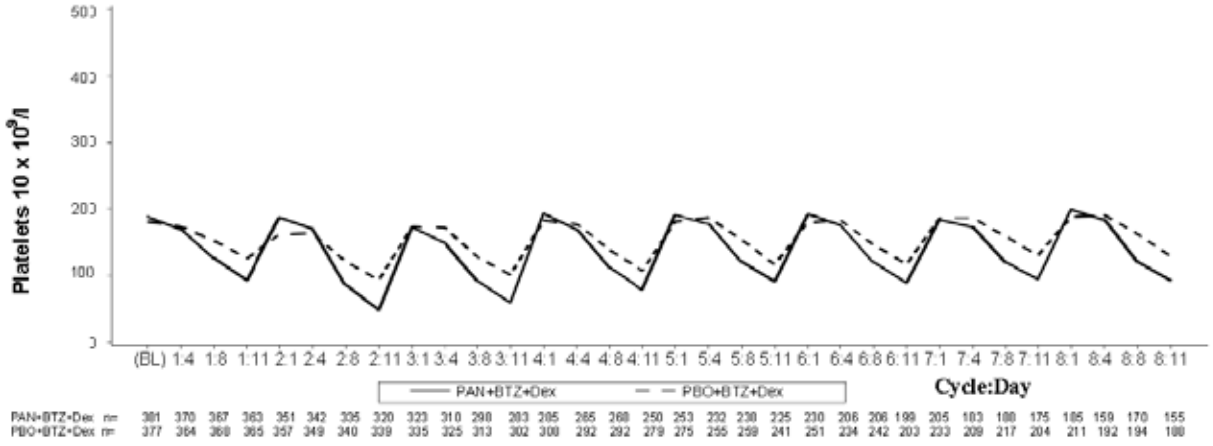
Due to the nature of multiple myeloma and the known haemato-toxicity for panobinostat and its combination agent bortezomib, thrombocytopenia, often severe, has been frequently observed (See Boxed Warning).

In the clinical trial in patients with relapsed multiple myeloma, 67% of patients treated with FARYDAK developed Grade 3 to 4 thrombocytopenia compared with 31% in the control arm and may be associated with an increased risk of serious and fatal haemorrhage (see Boxed Warning). Thrombocytopenia led to treatment interruption and or dose modification in 31% of patients receiving FARYDAK compared to 11% of patients in the control arm. For patients receiving FARYDAK, 33% required platelet transfusion compared to 10% of patients in the control arm.

Thrombocytopenia seldom led to treatment discontinuation (1.6% of patients). Most of patients with thrombocytopenia did not experience haemorrhage. There were 20.7% patients that experienced haemorrhage, most frequently epistaxis (4.7%), haematoma (2.6%), and conjunctival haemorrhage (2.1%) and uncommonly intracranial haemorrhage (0.6%). CTCAE grade 3-4 haemorrhage was reported in 4.2% of the patients, mostly commonly involving gastrointestinal haemorrhage.

In the Phase III study, thrombocytopenia typically recovered to baseline by the start of the next 21-day cycle. The median time to onset was one month and the median time to recovery was 12 days. Thrombocytopenia can usually be effectively managed by dose adjustment and interruption with or without platelet transfusion (see Dosage and Administration).

Figure 2 Median platelet counts over time (Study D2308, Safety set, cycles 1-8)



PAN= panobinostat, BTZ= bortezomib, Dex = dexamethasone

In patients with CTCAE grade 3 thrombocytopenia (platelet count <50 x 10^9/L with bleeding) FARYDAK may need to be temporarily withheld and/or the subsequent dose may need to be reduced. Platelet transfusions may be required as clinically indicated (see Dosage and Administration and Adverse Effects.

Neutropenia was frequently reported by laboratory findings during study (all grades: 75%). Severe neutropenia occurred in 34% of patients treated with FARYDAK, compared to 11% of patients in the control arm and may contribute to an increased risk of serious and fatal infections (see Boxed WARNING). Most of newly occurring severe neutropenia findings were grade 3 (28%) and much less grade 4 (6.6%). While many patients developed neutropenia, febrile neutropenia only occurred in a fraction of treated patients (1.0%, both in CTCAE grade all and grade 3-4). Patients with neutropenia are prone to infection, mostly upper respiratory tract infection or pneumonia. Only 0.3% of the patients discontinued the treatment due to neutropenia.

Neutropenia led to treatment interruption and or dose modification in 10% of patients receiving FARYDAK. The use of granulocyte-colony stimulating factor (G-CSF) was higher in patients treated with FARYDAK compared to the control arm, 13% compared to 4%, respectively.

Obtain a baseline complete blood count (CBC) and monitor the CBC weekly during treatment (or more frequently if clinically indicated). Dose modifications are recommended for myelosuppression (see Dosage and Administration). Monitor CBCs more frequently in patients over 65 years of age due to the increased frequency of myelosuppression in these patients (see Dosage and Administration, elderly patients (≥ 65 years).

The platelet count should be ≥100 x 10^9/L and the absolute neutrophil count should be

≥1.0 x 10^9/L prior to initiation of treatment. The platelet count should be ≥100 x 10^9/L prior to initiating any cycle of treatment (see Dosage and Administration).

Haemorrhage

Fatal and serious haemorrhage has been reported in patients during treatment with panobinostat. CTCAE grade 3-4 haemorrhage including cases of GI and pulmonary haemorrhage with fatal outcomes was reported (see Boxed Warning). In the clinical trial in patients with relapsed multiple myeloma, 5 patients receiving FARYDAK compared to 1 patient in the control arm died due to a haemorrhagic event. All 5 patients had grade ≥3 thrombocytopenia at the time of the event. Grade 3/4 haemorrhage was reported in 4% of patients treated with the FARYDAK arm and 2% of patients in the control arm. Therefore, physicians and patients should be aware of the increased risk of thrombocytopenia and the potential for haemorrhage, especially in patients with coagulation disorders, receiving chronic anticoagulation therapy.

Infection

Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, such as aspergillosis or candidiasis and viral infections including hepatitis B virus and herpes simplex, have been reported in patients taking FARYDAK. Potential contributing factors may include prior history of chemotherapy, stem cell transplant, the nature of the disease and neutropenia or lymphopenia associated with FARYDAK treatment. The most frequently reported infections include upper respiratory tract infection, pneumonia and nasopharyngitis. Some of these infections (e.g. pneumonia) have been severe (e.g. leading to sepsis, respiratory or multi organ failure) and have had fatal outcomes (see Adverse Effects). Of note, whereas grade 3 and grade 4 neutropenia were observed in 28% and 7% of patients respectively, febrile neutropenia was observed in 1% of patients (see Adverse Effects). Physicians and patients should be aware of the increased risk of infection with FARYDAK.

FARYDAK treatment should not be initiated in patients with active infections. Treat pre-existing infections prior to starting treatment with FARYDAK. Monitor patients for signs and symptoms of infections during treatment with FARYDAK; if a diagnosis of infection is made, institute appropriate anti-infective treatment promptly and consider interruption or discontinuation of FARYDAK. Treatment discontinuation due to infections was reported for 5% of the patients.

If a diagnosis of invasive systemic fungal infection is made, discontinue FARYDAK and treat with appropriate antifungal therapy.

Hepatotoxicity

Hepatic dysfunction, primarily mild transient elevations in aminotransferases and total bilirubin have been reported in patients during treatment with panobinostat.

Liver function should be monitored prior to treatment and regularly during treatment. If results of liver function tests show abnormalities according to the NCI CTEP classification, dose adjustments for patients with mild and moderate hepatic impairment are recommended and the patient should be followed until values return to normal or pre-treatment levels (see Dosage and Administration). Panobinostat should not be administered in patients with severe hepatic impairment due to lack of experience in this population.

Strong CYP3A4 inducers
Strong inducers may reduce the efficacy of panobinostat, therefore the concomitant use of strong CYP3A4 inducers should be avoided (see Interactions with other Medicines)

Use in the Elderly
It is recommended to monitor patients over 65 years of age more frequently, especially for thrombocytopenia and gastrointestinal toxicity (see Adverse Effects). For patients >75 years of age, depending on the patient's general condition and concomitant diseases, an adjustment of the starting doses or schedule of the components of the combination regimen may be considered (see Dose and Administration). The subgroup of heavily pre-treated patients for whom this medicine is approved for, included no patients over the age of 80 years and hence the benefit-risk in those over the age of 80 years is unknown.

Effects on Fertility
Based on non-clinical findings, male and female fertility may be compromised by treatment with FARYDAK.

In an oral fertility study conducted in rats, 10, 30 and 100 mg/kg doses of panobinostat were administered to males and females 3 times weekly (days 1, 3 and 5) for 4 (male) or 2 (female) weeks prior to mating, then during the mating period, and on gestation days 0, 3 and 6. Fertility index was decreased at 100 mg/kg (~4 times the clinical exposure based on AUC). An increase in early resorptions was observed at doses ≥30 mg/kg (approximately half the clinical exposure). Decreased maternal food consumption and body weight also occurred at these doses. The no effect level for fertility and early embryofetal development was 10 mg/kg (0.06 times the clinical exposure). Prostatic atrophy accompanied by reduced secretory granules, and testicular degeneration, oligospermia and increased epididymal debris were observed in repeated dose toxicity studies in dogs given doses of 1.0 - 1.5 mg/kg PO (0.4 the clinical exposure). These effects were not completely reversible following a 4-week recovery period. Oligospermia was also seen in a repeated dose toxicity study in rats at 100 mg/kg (2.2 times the clinical exposure).

Pregnancy – Category D
FARYDAK can cause fetal harm when administered to a pregnant woman. There are no clinical studies on the use of FARYDAK in pregnant patients.

Given its cytostatic/cytotoxic mode of action and fetal outcomes following exposure in pregnant animals that were lower than exposures observed in the clinical studies, there is a risk to the developing fetus. The patient should be advised of the risk to a fetus, if FARYDAK is used during pregnancy or if the patient becomes pregnant while taking this drug.

Studies in animals have shown embryo-fetal toxicity and teratogenicity.

Embryofetal development studies performed in pregnant rats given oral doses (30 – 300 mg/kg/day, ≥3 times the clinical exposure based on AUC) showed embryo-fetal-lethality, increases in skeletal variations and anomalies (extra vertebrae, extra ribs, cleft palate, short tail and increases in minor skeletal variations). The doses also produced maternal toxicity and decreases in fetal body weight. In rabbits, embryo-fetal lethality and increases in skeletal anomalies (extra sternabrae, extra ribs, increases in minor skeletal variations, delayed ossification, and variations of the sternabrae) were seen at ≥40 mg/kg/day (≥3 times the clinical exposure) and malformations (interventricular septal defect, interrupted aortic arch, missing gallbladder and missing forepaw digit) at 80 mg/kg/day (6 times the clinical exposure). Decreases in fetal body weight and maternal toxicity were also observed. The NOAELs for these findings in pregnant rabbits was 10 mg/kg/day (0.5 times the clinical exposure).

Labour and delivery
No data in humans are available. The effects of panobinostat on labour and post-natal growth and maturation were not evaluated in animal studies.

Women of child-bearing potential and contraceptive measures

Pregnancy testing:
Sexually-active females of reproductive potential should have a pregnancy test prior to the initiation of treatment with FARYDAK.

Contraception:

Females of reproductive potential should be advised that animal studies have shown FARYDAK to be harmful to the developing fetus. Women of child-bearing potential should be advised to use a highly effective method of contraception (methods that result in less than 1% pregnancy rates) during treatment with FARYDAK and for 3 months after the last dose of FARYDAK.

If medicinal products that decrease the efficacy of hormonal contraceptives are taken concomitantly, an alternative highly effective method of contraception should be used.

Males of reproductive potential
Sexually active men must use a condom during intercourse with females of reproductive potential or pregnant women while on treatment and for -6 months after their last dose of

FARYDAK to avoid conception or embryo-fetal harm. Female partners of sexually active men should also use a highly effective contraceptive method (methods that result in less than 1% pregnancy rates) during treatment and for 6 months after their male partner has stopped taking FARYDAK.

Use in Lactation
It is unknown whether panobinostat is excreted in human milk, and no animal studies were conducted that measured panobinostat concentrations in milk. There are no data on the effects of FARYDAK on the breastfed child or the effects of FARYDAK on milk production. Given the potential for serious adverse drug reactions in breastfed newborns/infants from FARYDAK, a nursing woman should be advised on the potential risks to the child. A decision should be made whether to abstain from breast feeding or to abstain from using FARYDAK treatment, taking into account the importance of the FARYDAK to the mother.

Genotoxicity
Panobinostat was mutagenic in the Ames assay, caused endo-reduplication in human peripheral blood lymphocytes *in vitro*, and DNA damage in a COMET assay mouse lymphoma L5178Y cells.

Carcinogenicity
Carcinogenicity studies have not been performed with panobinostat.

Interactions with Other Medicines

FARYDAK metabolism is primarily through non-CYP and CYP mediated routes. Approximately 40% of panobinostat is metabolized through CYP3A4, with minor involvement of CYP2D6 and 2C19.

In vitro, panobinostat is a competitive inhibitor of CYP2D6 (K_i 0.167 μM), and a weak time-dependent CYP3A4 inhibitor (K_I value of 12 μM and k_{inact} value of 0.0228 min^{-1}). It increased the plasma exposure of a CYP2D6 substrate dextromethorphan.

Panobinostat is a P-gp substrate and not an inhibitor of P-gp. P-gp inhibitors and inducers may alter the distribution of the parent drug into tissues which expresses P-gp and potentially affect plasma concentrations of panobinostat. Panobinostat has little to no inhibitory activity against uptake transporters OAT1, OAT3, OCT1, OCT3, OATP1B1 and OATP1B3 (IC_{50}s>4 μM).

Agents that may increase panobinostat blood concentrations
CYP3A Inhibitors: Co-administration of a single 20 mg panobinostat dose with ketoconazole, a strong CYP3A inhibitor, increased the Cmax and AUC of panobinostat by 1.6- and 1.8 respectively, compared to when panobinostat was given alone.

Reduce panobinostat dose to 10 mg when coadministered with strong CYP3A inhibitors, which include but are not limited to ketoconazole, itraconazole, voriconazole, ritonavir, boceprevir, clarithromycin, conivaptan, indinavir, saquinavir, telaprevir, telithromycin, posaconazole, and nefazodone, nelfinavir, lopinavir/ritonavir. Clinical monitoring is recommended when FARYDAK is co-administered with strong CYP3A inhibitors.

Patients should be instructed to avoid star fruit, pomegranates or pomegranate juice, Seville oranges, grapefruit or grapefruit juice as these foods are known to inhibit cytochrome CYP450 3A enzymes and may increase the bioavailability of panobinostat.

Agents that may decrease panobinostat plasma concentrations
CYP3A Inducers: Panobinostat fraction metabolized through CYP3A4 is approximately 40%. Co-administration of FARYDAK with strong CYP3A inducers was not evaluated *in vitro* or in a clinical trial however, a reduction in panobinostat exposure is likely. An approximately 70% decrease in the systemic exposure of panobinostat in the presence of strong inducers of CYP3A was observed in simulations using mechanistic models. In clinical studies in multiple myeloma, the exposure of panobinostat was decreased by 20-50% by the concomitant use of dexamethasone which is a dose-dependent mild/moderate CYP3A4 inducer. Therefore, the concomitant use of strong CYP3A4 inducers should be avoided.

Agents whose plasma concentrations may be increased by panobinostat
CYP2D6 Substrates: Panobinostat increased the Cmax and the AUC of dextromethorphan (a sensitive substrate of CYP2D6) by 1.8- and 1.6-fold, respectively; however this was highly variable. Avoid co-administrating FARYDAK with sensitive CYP2D6 substrates (i.e., atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, and venlafaxine) or CYP2D6 substrates that also have a narrow therapeutic index (including, but not limited tothioridazine and pimozide) should be avoided.

If concomitant use of sensitive CYP2D6 substrates is unavoidable, monitor patients frequently for adverse reactions.

CYP3A Substrates: Simulations using PBPK models predict that an exposure increase of less than 10% for the sensitive CYP3A substrate midazolam is likely following coadministration with panobinostat. The clinical implications of this finding are not known.

Drugs that prolong QT interval
Based on preclinical and clinical data, panobinostat has the potential to prolong the QT interval. Concomitant use of anti-arrhythmic medicines (including - but not limited to - amiodarone, disopyramide, procainamide, quinidine and sotalol) and other drugs that are known to prolong the QT interval (including, but not limited to chloroquine, halofantrine, clarithromycin, methadone, moxifloxacin, bepridil and pimozide) are not recommended. Anti-emetic drugs with

a known QT prolongation risk, such as dolasetron, ondansetron and tropisetron should be used with caution (see Precautions).

Adverse Effects

Summary of the safety profile

The safety data reported below are based on the phase III clinical study in patients with multiple myeloma, treated with 20 mg panobinostat once a day three times per week, on a 2 weeks on 1 week off dosing regimen in combination with bortezomib and dexamethasone.

The median duration of exposure to drug was 5.0 months. 15.7 % of patients were exposed to study treatment for > 48 weeks.

Diarrhoea (68.2%), thrombocytopenia (64.6%), anaemia (41.5%), fatigue (41.2%), and nausea (36.2%) were the most commonly occurring AEs in the PAN+BTZ+Dex treatment arm and were each reported in >36.0% of patients.

The most common non-haematologic adverse reactions were diarrhoea, fatigue, nausea, and vomiting. Treatment emergent haematologic toxicities included thrombocytopenia, anaemia, neutropenia, leukopenia and lymphopenia (see Table 3 for laboratory abnormalities).

QTcF >480 < 500 msec was recorded in 1.3% of patients and change from baseline of >60 msec was observed in 0.8% of patients. No patient had an absolute QTcF >500 msec.

Discontinuation due to AEs was higher in patients receiving PAN+BTZ+Dex combination therapy (138 patients, 36.2%) compared to those patients in the PBO+BTZ+Dex arm (77 patients, 20.4%).

The overall incidence of AEs requiring dose adjustments or treatment interruptions was 88.7% in the PAN+BTZ+Dex group and 75.6% in the PBO+BTZ+Dex group.

On-treatment deaths, regardless of causality, were reported in 7.9% of PAN+BTZ-Dex-treated patients vs. 4.8% of PBO+BTZ+Dex-treated patients. The most frequent treatment related causes of death included infections and haemorrhage. Cardiac disorders were reported in 1.0% of PAN+BTZ-Dex-treated patients vs. 0.8% in PBO+BTZ+Dex. One case was reported as suspected to study drug involved a patient whose medical history included arrhythmia and left ventricular hypertrophy but with no apparent ECG abnormalities reported during the study died of massive myocardial infarction.

Tabulated list of adverse drug reactions from clinical studies

Adverse drug reactions from the phase III study (D2308) are shown in Table 2. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is

based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from available data).

Table 2 Adverse drug reactions observed in multiple myeloma patients in the phase III (D2308) study

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Very common	Upper respiratory tract infection, pneumonia
	Common	Septic shock, urinary tract infection, viral infection, oral herpes, *Clostridium difficile* colitis, otitis media, cellulitis, sepsis, gastroenteritis, lower respiratory tract infection, candidiasis
	Uncommon	Pneumonia fungal, hepatitis B, aspergillosis
Blood and lymphatic system disorders[a]	Very common	Pancytopenia, thrombocytopenia, anaemia, leukopenia, neutropenia, lymphopenia
Endocrine disorders	Common	Hypothyroidism
Metabolism and nutrition disorders	Very common	Decreased appetite, hypophosphataemia[a], hyponatraemia[a], hypokalaemia[a]
	Common	Hyperglycaemia, dehydration, hypoalbuminaemia, fluid retention, hyperuricaemia, hypocalcaemia, hypomagnesaemia
Psychiatric disorders	Very common	Insomnia
Nervous system disorders	Very common	Dizziness, headache
	Common	Syncope, tremor, dysgeusia
	Uncommon	Haemorrhage intracranial
Eye disorders	Common	Conjunctival haemorrhage
Cardiac disorders	Common	Bradycardia, atrial fibrillation, sinus tachycardia, tachycardia, palpitation
	Uncommon	Myocardial infarction
Vascular disorders	Very common	Hypotension
	Common	Hypertension, haematoma, orthostatic hypotension
	Uncommon	Shock haemorrhagic
Respiratory, thoracic and mediastinal disorders	Very common	Cough, dyspnoea
	Common	Respiratory failure, rales, wheezing, epistaxis
	Uncommon	Pulmonary haemorrhage, haemoptysis
Gastrointestinal disorders	Very common	Diarrhoea, nausea, vomiting, abdominal pain, dyspepsia

System Organ Class	Frequency	Adverse reaction
	Common	Gastrointestinal haemorrhage, haematochezia, gastritis, cheilitis, abdominal distension, dry mouth, flatulence
	Uncommon	Colitis, haematemesis, gastrointestinal pain
Hepatobiliary disorders	Common	Hepatic function abnormal, hyperbilirubinaemia[a]
Skin and subcutaneous disorders	Common	Skin lesions, rash, erythema
	Uncommon	Petechiae
Musculoskeletal and connective tissue disorders	Common	Joint swelling
Renal and urinary disorders	Common	Renal failure, haematuria, urinary incontinence
General disorders and administration site conditions	Very common	Fatigue, oedema peripheral, pyrexia, asthenia
	Common	Chills, malaise
Investigations	Very common	Weight decreased
	Common	Blood urea increased, glomerular filtration rate decreased, blood alkaline phosphatase increased, electrocardiogram QT prolonged, blood creatinine increased[a], SGPT alanine transaminase (ALT) increased[a], SGOT aspartate transaminase (AST) increased[a]
[a] Frequency is based on laboratory values		

Laboratory abnormalities

Clinically relevant or severe abnormalities of routine haematological or biochemical laboratory values are presented in Table 3.

Table 3 Laboratory abnormalities (≥10% Incidence and ≥5% Greater Incidence in FARYDAK-arm) in multiple myeloma patients observed in the phase III trial

Laboratory abnormalities	Panobinostat, BTZ[1], Dex[2] N=381 (%) all grades	Placebo, BTZ[1], Dex[2] N=377 (%) all grades	Panobinostat, BTZ[1], Dex[2] N=381 (%) grade 3-4	Placebo, BTZ[1], Dex[2] N=377 (%) grade 3-4	Frequency Category (overall)
Haematological parameters					
Thrombocytopenia	98	84	67	31	Very common
Anaemia	62	52	18	19	Very common
Leukopenia	81	48	23	8	Very common
Neutropenia	75	36	35	11	Very common
Lymphopenia	83	73	53	40	Very common
Biochemistry parameters					
Blood creatinine increased	41	23	1	2	Very common
Hypokalemia	53	36	18	7	Very common
Hypophosphatemia	64	46	20	12	Very common
Hyponatremia	49	36	14	7	Very common

Laboratory abnormalities	Panobinostat, BTZ[1], Dex[2] N=381 (%) all grades	Placebo, BTZ[1], Dex[2] N=377 (%) all grades	Panobinostat, BTZ[1], Dex[2] N=381 (%) grade 3-4	Placebo, BTZ[1], Dex[2] N=377 (%) grade 3-4	Frequency Category (overall)
Hyperbilirubinemia	21	13	<1	<1	Very common
SGPT Alanine amino transaminase (ALT) increased	31	38	2	1	Very common
SGOT Aspartate amino transaminase (AST) increased	31	28	2	1	Very common

[1] BTZ = bortezomib; [2] Dex = dexamethasone

Description of selected Adverse Drug Reactions
Fatigue and asthenia

Fatigue and asthenia were reported in 41.2% and 22.0% of the patients, respectively. CTCAE grade 3 fatigue was reported in 15.7% of the patients, and grade 4 in 1.3%. Grade 3 asthenia was observed in 9.4% of the patients, with no patients experiencing asthenia at CTCAE grade 4. Treatment discontinuation due to fatigue or asthenia was reported in 2.9% of the patients each.

Special population

Elderly patients

In patients over 65 years of age the incidence of deaths not related to study indication was 8.8% in patients ≥ 65 years of age compared to 5.4 % in patients < 65 %.

Adverse reactions leading to permanent discontinuation occurred in 30%, 44% and 47% of patients aged <65 years, 65 - 75 years and ≥75 years, respectively. Grade 3 - 4 events more frequently observed in patients included the following (percentages presented for patients <65 years, 65 - 75 years and ≥75 years of age, respectively): thrombocytopenia (60%, 74%, and 91%), anaemia (38%, 44% and 62%), diarrhoea (21%, 27% and 47%), and fatigue (18%, 28% and 47%).

Dosage and Administration

Treatment should be initiated and monitored by a specialist with experience in treating haematological malignancies. The recommended starting dose of FARYDAK is 20 mg, taken orally once a day, on days 1, 3, 5, 8, 10 and 12, of a 21 days cycle. Patients should be treated initially for eight cycles. It is recommended that patients with clinical benefit continue the treatment for eight additional cycles. The total duration of treatment is up to 16 cycles (48 weeks).

FARYDAK capsules should be administered orally once daily at the same time each day. Capsules should be swallowed whole with water. FARYDAK can be taken with or without food however it is recommended it be taken on a full stomach in order to reduce the risks of nausea and vomiting (see Pharmacology).

FARYDAK capsules should not be opened, crushed or chewed. If a dose is missed, it can be taken up to 12 hours after the specified dose time. If vomiting occurs the patient should not take an additional dose, but should take the next usual prescribed dose.

The recommended dose of bortezomib is 1.3 mg/m^2 given as an injection. The recommended dose of dexamethasone is 20 mg taken orally, on a full stomach.

The maximum tolerated dose (MTD) was established at panobinostat 20 mg plus bortezomib 1.3 mg/m^2 in patients with relapsed or relapsed and refractory multiple myeloma.

FARYDAK is administered in combination with bortezomib and dexamethasone as shown in Table 4 and Table 5.

Table 4 Recommended dosing schedule of FARYDAK in combination with bortezomib and dexamethasone (cycles 1-8)

Cycles 1-8 (3 week cycles)	Week 1 Days							Week 2 Days							Week 3
FARYDAK	1		3		5			8		10		12			Rest period
Bortezomib	1			4				8			11				Rest period
Dexamethasone	1	2		4	5			8	9		11	12			Rest period

Table 5 Recommended dosing schedule of FARYDAK in combination with bortezomib and dexamethasone (cycles 9-16)

Cycles 9-16 (3 week cycles)	Week 1 Days							Week 2 Days							Week 3
FARYDAK	1		3		5			8		10		12			Rest period
Bortezomib	1							8							Rest period
Dexamethasone	1	2						8	9						Rest period

Monitoring recommendations

Blood cell counts: a complete blood cell count must be performed before initiating treatment with FARYDAK. The baseline platelet count should be ≥100 x 10^9/L and the baseline absolute neutrophil count (ANC) ≥1.0 x 10^9/L. Complete blood counts should be monitored weekly (or more frequently if clinically indicated) during treatment, especially for thrombocytopenia (see Precautions). Prior to initiating any cycle of therapy with FARYDAK in combination with bortezomib and dexamethasone, the platelet count should be at least ≥100 x 10^9/L (see Precautions).

ECG: FARYDAK may increase the QTc interval (see Precautions). Therefore an ECG should be recorded prior to the start of therapy and repeated periodically before each treatment cycle. QTcF should be <450 msec prior to initiation of treatment with FARYDAK (see dose modifications below and Precautions).

Blood electrolytes: blood electrolytes, especially potassium, magnesium and phosphorus, should be measured at baseline and monitored periodically. Abnormal values should be corrected as clinically indicated (see Precautions).

Liver function tests: Liver function should be monitored prior to treatment and regularly during treatment as clinically indicated, especially in patients with hepatic impairment (see Precautions).

Dose modifications

Treatment dose and/or schedule modification may be required based on individual tolerability.

If a dose reduction is required, the dose of FARYDAK should be reduced by decrements of 5 mg, (i.e. from 20 to 15 mg, or from 15 to 10 mg). The dose should not be reduced below 10 mg daily. Keep the same treatment schedule (three week treatment cycle).

FARYDAK is administered in combination with bortezomib and dexamethasone. The bortezomib and dexamethasone prescribing information should be consulted prior to starting the combination treatment.

Thrombocytopenia

Platelet counts should be monitored prior to each dose of bortezomib (BTZ) (i.e., on days 1, 4, 8 and 11 of cycles 1-8, see Table 4, and on days 1 and 8 of cycles 9-16 see Table 5). If patients experience thrombocytopenia (TCP), FARYDAK may need to be temporarily withheld and the subsequent dose may need to be reduced as outlined in Table 6.

Table 6 Recommended dose modifications for thrombocytopenia

CTCAE grade on day of treatment	Action PAN	PAN dose on recovery to Thrombocytopenia (TCP) ≤ grade 2 (≥50 x 10^9/L)	Action BTZ	BTZ dose on recovery to grade 2 TCP (≥50x10^9/L)	
				1 dose omitted	More than 1 dose omitted
Thrombocytopenia Grade 3 (<50 x 10^9 /L) with bleeding	Omit dose. Monitor platelet counts at least weekly until ≥50 x 10^9/L	Resume at reduced dose	Omit dose	Resume at same dose	Resume at reduced dose
Thrombocytopenia Grade 4(<25 x 10^9/L)					

Platelet transfusions may be required if clinically indicated (see Precautions). Discontinuation of treatment may be considered if thrombocytopenia does not improve despite the treatment modifications described above and/or the patient requires repeated platelet transfusions.

Gastrointestinal toxicity

Gastrointestinal toxicity is very common in patients treated with FARYDAK. Patients who experience diarrhoea and nausea or vomiting may require temporary dose discontinuation or dose reduction as outlined in Table 7.

Table 7 Recommended dose modifications for GI toxicities

Adverse drug reaction	CTCAE grade on day of treatment	PAN Action	PAN Dose upon recovery to ≤grade 1	Modification of BTZ starting dose	BTZ dose on recovery to ≤grade 1
Diarrhoea	grade 2 despite anti-diarrhoeal medications	Omit dose	Resume at the same dose	Omit dose	Resume at same dose or with the same dose but with a once-weekly

Adverse drug reaction	**CTCAE grade on day of treatment**	**PAN Action**	**PAN Dose upon recovery to ≤grade 1**	**Modification of BTZ starting dose**	**BTZ dose on recovery to ≤grade 1**
					schedule
	grade 3 despite anti-diarrhoeal medications	Omit dose	Resume at reduced dose	Omit dose	Resume at reduced dose or with the same dose but with a once-weekly schedule
	grade 4 despite anti-diarrhoeal medications	Discontinue		Discontinue	
Nausea or Vomiting	Nausea grade 3 or Vomiting grade 3-4 despite antiemetic medications	Omit dose	Resume at reduced dose		

At the first sign of abdominal cramping, loose stools, or onset of diarrhoea, it is recommended that the patient be treated with anti-diarrhoeal medication (eg loperamide). Prophylactic anti-emetics should be administered at the discretion of the physician and in accordance with local medical practice (see Precautions).

Neutropenia

Neutropenia may require temporary or permanent dose reduction. Instructions for dose interruptions and reductions for Farydak and bortezomib are outlined in Table 8.

Table 8 Recommended dose modifications for neutropenia

CTCAE grade on day of treatment	**PAN Action**	**PAN Dose upon recovery to Neutropenia grade 2 (<1.5 – 1.0 x 10^9 /L)**	**Modification of BTZ starting dose**	**BTZ dose on recovery to grade 2 neutropenia (<1.5-1.0 x 10^9/L)**
Neutropenia Grade 3 (<1.0 – 0.5 x 10^9 /L)	Omit dose	Resume at same dose	Omit dose	Resume at same dose
Neutropenia Grade 4 (<0.5x10^9/L) or Febrile neutropenia Grade 3 (<1.0 x10^9/L and fever ≥38.5°C)	Omit dose	Resume at reduced dose	Omit dose	Resume at same dose

In case of grade 3 or 4 neutropenia, physicians should consider the use of growth factors (e.g. G-CSF) according to local guidelines. Discontinuation of treatment may be considered if neutropenia does not improve despite the dose modifications and/or despite the addition of colony stimulating factor therapy according to local medical practice and treatment guidelines, and/or in case of severe secondary infections.

QTc prolongation

In case of long QT interval prior to the start of dosing with FARYDAK (QTcF ≥ 450 msec at baseline), the start of the treatment should be delayed until the pre-dose average QTcF has returned to <450 msec. In addition, any abnormal serum potassium, magnesium and phosphorus values should be corrected prior to the start of FARYDAK therapy (see Precautions). In case of QT prolongation during treatment see Table 9 below.

Table 9 Recommended dose modifications for QTc prolongation

QTc prolongation on day of treatment	**Action**		**Resolution within 7 days**		**Unresolved within 7 days**
	Initial occurrence	**Recurrent**	**Initial occurrence**	**Recurrent**	**Initial/Recurrent**
QTcF is ≥ 480 msec or above 60 msec from baseline	Omit dosing	Omit dosing	Resume at same dose	Resume at reduced dose	Discontinue

QTcF value is above 500 msec	Discontinue	---	---	---	---

Other adverse events

For patients experiencing severe adverse events other than thrombocytopenia, neutropenia, QTc prolongation or gastrointestinal toxicity, the recommendation is provided in the following Table 10.

Table 10 Guide to Managing other CTCAEs

CTCAE Grade	**Action**		**Dose upon recovery to ≤ grade 1**	**Dose upon recovery to < grade 1**
	Initial occurrence	**Recurrent**		
CTCAE grade 2 toxicity	--------	Omit dosing	Resume at reduced dose	------
CTCAE grade 3 and 4 toxicity	Omit dosing	Omit dosing	-------	Consider a *further* dose reduction

Strong CYP3A inhibitors

In patients who take concomitant medicinal products which are strong CYP3A inhibitors the dose of panobinostat should be reduced to 10 mg (see Interactions with other medicines).

Special populations

Patients with renal impairment: Plasma exposure of panobinostat is not altered in cancer patients with mild to severe renal impairment. Therefore, starting dose adjustments are not necessary. Panobinostat has not been studied in patients with end stage renal disease (ESRD) or patients on dialysis (see Pharmacology and Precautions).

Patients with hepatic impairment: Clinical study in patients with impaired hepatic function has shown that plasma exposure of panobinostat increased by 43% (1.4-fold) and 105% (2-fold), in patients with mild and moderate hepatic impairment, respectively. No experience with FARYDAK is available in patients with severe hepatic impairment. Avoid use in patients with severe hepatic impairment.

Caution should be exercised in patients with hepatic impairment. Reduce the starting dose of FARYDAK to 15 mg in patients with mild hepatic impairment and 10 mg in patients with moderate hepatic impairment. Monitor patients frequently for adverse events and adjust dose as needed for toxicity (see Pharmacology,Precautions and Monitoring Recommendations).

Paediatric patients: No studies have been performed and there is no relevant use of FARYDAK in paediatric patients below the age of 18 in the indication of multiple myeloma (see Pharmacology).

Elderly patients (≥ 65 years): More than 40% of patients in the Phase III clinical study were ≥65 years of age, with no evidence suggesting adjustment of the starting dose (see Pharmacology). A consistent benefit was observed, however, patients over 65 years of age had a higher frequency of selected adverse events and of discontinuation of treatment because of adverse events. It is recommended to monitor the patients over 65 years of age more frequently, especially for thrombocytopenia and gastrointestinal toxicities (see Adverse Effects for more details).

Elderly patients (>75 years): For patients >75 years of age, depending on the patient's general condition and concomitant diseases, an adjustment of the starting doses or schedule of the components of the combination regimen may be considered. Panobinostat may be started at a dose of 15 mg, and if tolerated in the first cycle escalated to 20 mg in the second cycle. Bortezomib may be started at 1.3 mg/m^2 once weekly on days 1 and 8, and dexamethasone at 20 mg on days 1 and 8.

Overdosage

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

Limited experience with overdose has been reported during clinical trials. Adverse reactions observed were consistent with the safety profile with primarily events involving hematologic and GI disorders such as thrombocytopenia, pancytopenia, diarrhoea, nausea, vomiting and anorexia. Cardiac monitoring and assessment of electrolytes and platelet counts should be undertaken and supportive care given as necessary in the event of overdose. It is not known if panobinostat is dialyzable.

Presentation and storage conditions

10 mg hard capsule: Size # 3 light green opaque capsule, radial markings on cap with black ink "LBH 10 mg" and two radial bands with black ink on body, containing white to almost white powder.

15 mg hard capsule: Size #1 orange opaque capsule, radial markings on cap with black ink "LBH 15 mg" and two radial bands with black ink on body, containing white to almost white powder.

20 mg hard capsule: Size #1 red opaque capsule, radial markings on cap with black ink "LBH 20 mg" and two radial bands with black ink on body, containing white to almost white powder.

The hard capsules are contained in PVC/PCTFE blister packs and packaged into cardboard cartons. FARYDAK 10 mg, 15 mg and 20 mg hard capsule pack sizes include 6, 12*, and 24*.

*Not all pack sizes are marketed.

Store below 30° C. Store in the original container in order to protect from moisture.

Name and Address of Sponsor

Novartis Pharmaceuticals Australia Pty Ltd

54 Waterloo Road

Macquarie Park, 2113 NSW

Australia

Poison Schedule of the Medicine

(S4) Prescription Only Medicine.

Date of First Inclusion in the Australia Register of Therapeutic Goods (the ARTG)

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