NOVARTIS

Farydak ®

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Hard gelatin capsules

10 mg 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 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 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.

Active substance

Panobinostat lactate anhydrous

(2E)-N-Hydroxy-3-[4-({[2-(2-methyl-1H-indol-3-yl)ethyl]amino}methyl)phenyl]prop-2-enamide 2-hydroxypropanoate (1:1)

10 mg capsule: Each capsule contains 10 mg panobinostat free base, corresponding to 12.576 mg of panobinostat lactate anhydrous

15 mg capsule: Each capsule contains 15 mg panobinostat free base, corresponding to 18.864 mg panobinostat lactate anhydrous

20 mg capsule: Each capsule contains 20 mg panobinostat free base, corresponding to 25.152 mg panobinostat lactate anhydrous

Active moiety

Panobinostat

Excipients

Capsule content: Magnesium stearate, mannitol, microcrystalline cellulose, pregelatinized starch.

Capsule shell:

Gelatin, Titanium dioxide (E171, CI 77891), Brilliant blue FCF- FD&C Blue 1(E133, CI 42090), Yellow iron oxide (E172, CI 77492) for 10 mg strength

Gelatin, Titanium dioxide (E171, CI 77891), Yellow iron oxide (E172, CI 77492), Red iron oxide / Ferric oxide red (E172, CI 77491) for 15 mg strength

Gelatin, Titanium dioxide (E171, CI 77891), Red iron oxide / Ferric oxide red (E172, CI 77491) for 20 mg strength

Ink: Ammonium hydroxide, Black iron oxide (E172, CI 77499), isopropyl alcohol, N-butyl alcohol, propylene glycol (E1520), shellac glaze in ethanol

Pharmaceutical formulations may vary between countries.

INDICATIONS

Farydak, a histone deacetylase inhibitor, 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.

DOSAGE AND ADMINISTRATION

Treatment with Farydak should be initiated by a physician experienced in the use of anticancer therapies.

General Target Population

The recommended starting dose of panobinostat 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).

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.

Panobinostat is administered in combination with bortezomib and dexamethasone as shown in Table 1 and Table 2.

Table 1 Recommended dosing schedule of panobinostat 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 2 Recommended dosing schedule of panobinostat 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 panobinostat. 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 frequently monitored during treatment (in particular before each injection of bortezomib, i.e. on days 1, 4, 8 and 11 of cycles 1 to 8 and on days 1 and 8 of cycles 9 to 16), especially for thrombocytopenia (see section WARNINGS AND PRECAUTIONS). Prior to initiating any cycle of therapy with panobinostat in combination with bortezomib and dexamethasone, the platelet count should be at least ≥100 x 10^9/L. (see section WARNINGS AND PRECAUTIONS). Additional blood counts should be considered during the 'rest period' – e.g. on days 15 and/or 18, especially in patients ≥65 years and patients with a baseline platelet count below 150 x 10^9/L.

ECG: Panobinostat may increase the QTc interval (see section WARNING AND PRECAUTIONS). Therefore an ECG should be recorded prior to the start of therapy and repeated periodically before each treatment cycle. QTcF should be <480 msec prior to initiation of treatment with panobinostat (see dose modifications below and section WARNINGS AND PRECAUTIONS).

Blood electrolytes: blood electrolytes, especially potassium, magnesium and phosphorus, should be measured at baseline and monitored periodically as clinically indicated, especially in patients with diarrhoea. Abnormal values should be corrected as clinically indicated (see section WARNINGS AND 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 section WARNING AND PRECAUTIONS).

Thyroid function tests: Mild hypothyroidism was reported in patients treated with panobinostat + bortezomib + dexamethasone in Study D2308; some patients required treatment (see section WARNING AND PRECAUTIONS). Thyroid and pituitary function should be monitored by measuring hormone levels (e.g. free T4 and TSH) as clinically indicated.

Dose modifications

Treatment dose and/or schedule modification may be required based on individual tolerability. Clinical judgment on how to continue the treatment should be exercised when a patient experiences adverse drug reactions.

If a dose reduction is required, the dose of panobinostat 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).

Panobinostat 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 1, and on days 1 and 8 of cycles 9-16 see Table 2). If patients experience thrombocytopenia (TCP), Panobinostat may need to be temporarily withheld and the subsequent dose may need to be reduced. In patients with Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) grade 3 ($<50x10^9$/L, complicated by bleeding), or grade 4 ($<25x10^9$/L) thrombocytopenia, panobinostat therapy should be withheld and resumed at a reduced dose upon recovery to ≤ grade 2 ($\geq 50 \times 10^9$/L). Platelet counts should be monitored at least twice a week until $\geq 50x10^9$/L. Also, the dose of bortezomib should be omitted in case of TCP grade 3 with bleeding or grade 4; it is recommended that after the first omitted BTZ, dosing of BTZ could be resumed at the same dose, whereas if more than one dose has been omitted, the restarting dose should be reduced one level. Platelet transfusions may be required if clinically indicated (see section WARNINGS AND 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.

Table 3 Recommended dose modifications for thrombocytopenia

Thrombocytopenia grade on day of treatment	**Modification of panobinostat starting dose**	**Panobinostat dose on recovery to ≤ grade 2 thrombocytopenia ($\geq 50 \times 10^9$/L)**	**Modification of bortezomib starting dose**	**Bortezomib dose on recovery to grade 2 thrombocytopenia ($\geq 50x\ 10^9$/L)**	
				1 dose omitted	**More than 1 dose omitted**
Grade 3 with bleeding Platelets $<50 \times 10^9$/L	Omit dose	Resume at reduced dose	Omit dose	Resume at same dose	Resume at reduced dose
Grade 4 Platelets $<25 \times 10^9$/L	Omit dose	Resume at reduced dose	Omit dose	Resume at same dose	Resume at reduced dose

Gastrointestinal toxicity

Gastrointestinal toxicity is very common in patients treated with panobinostat. Patients who experience diarrhea and nausea or vomiting may require temporary dose discontinuation or dose reduction as outlined in Table 4.

Table 4 Recommended dose modifications for gastrointestinal toxicity

Adverse drug reaction	Grade on day of treatment	Modification of panobinostat starting dose	Panobinostat dose on recovery to ≤ grade 1	Modification of bortezomib starting dose	Bortezomib dose on recovery to ≤ grade 1
Diarrhoea	Grade 2 despite anti-diarrheal medicinal product	Omit dose	Resume at the same dose	Omit dose	Resume at reduced dose or with the same dose but with a once-weekly schedule
	Grade 3 despite anti-diarrheal medicinal product	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-diarrheal medicinal product	Discontinue		Discontinue	

At the first sign of abdominal cramping, loose stools, or onset of diarrhea, it is recommended that the patient be treated with anti-diarrheal medication (e.g. loperamide). Prophylactic anti-emetics should be administered at the discretion of the physician and in accordance with local medical practice (see Section WARNINGS AND PRECAUTIONS). In the event of grade 3 nausea or grade 3 or 4 vomiting despite administration of an anti-emetic, panobinostat should be temporarily discontinued and resumed at a reduced dose on recovery to grade 1.

Neutropenia

Neutropenia may require temporary or permanent dose reduction. Instructions for dose interruptions and reductions for panobinostat and bortezomib are outlined in Table 5.

Table 5 Recommended dose modifications for neutropenia

Neutropenia grade on day of treatment	Modification of panobinostat starting dose	Panobinostat dose on recovery to grade 2 neutropenia (<1.5-1.0 x 10^9/L)	Modification of bortezomib starting dose	Bortezomib dose on recovery to grade 2 neutropenia (<1.5-1.0 x 10^9/L)
Grade 3 neutropenia (<1.0-0.5 x 10^9/L)	Omit dose	Resume at same dose	Omit dose	Resume at same dose
Grade 4 neutropenia (<0.5 x 10^9/L) or febrile neutropenia (<1.0 x 10^9/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 panobinostat (QTcF ≥ 480 msec at baseline), the start of the treatment should be delayed until the pre-dose average QTcF has returned to <480 msec. In addition, any abnormal serum potassium, magnesium and phosphorus values should be corrected prior to the start of panobinostat therapy (see section WARNINGS AND PRECAUTIONS). In case of QT prolongation during treatment:

- The dose should be omitted, if QTcF is ≥ 480 msec or above 60 msec from baseline.
- If QT prolongation is resolved within 7 days, resume treatment at prior dose for initial occurrence or at reduced dose if QT prolongation is recurrent.
- If QT prolongation is unresolved within 7 days, treatment should be discontinued.
- If any QTcF value is above 500 msec, panobinostat therapy should be permanently discontinued.

Other adverse drug reactions

For patients experiencing severe adverse drug reactions other than thrombocytopenia, neutropenia, QTc prolongation or gastrointestinal toxicity, the recommendation is the following:

- CTCAE grade 2 toxicity recurrences or CTCAE grade 3 and 4 - omit the dose until recovery to CTCAE grade ≤1 and resume treatment at a reduced dose.
- CTCAE grade 3 or 4 toxicity recurrence, a further dose reduction may be considered once the adverse events have resolved to CTCAE grade ≤1.

Strong CYP3A inhibitors

In patients who take concomitant medicinal products which are strong CYP3A and/or Pgp inhibitors the dose of panobinostat should be reduced to 10 mg (see section INTERACTIONS). If continuous treatment with a strong CYP3A4 inhibitor is required, a dose escalation from 10 mg to 15 mg panobinostat may be considered based on patient tolerability.

In patients with hepatic impairment receiving concomitant medicinal products which are strong CYP3A4 inhibitors, treatment with panobinostat should be avoided due to lack of experience and safety data in this patient population.

Strong CYP3A inhibitors should not be started in patients who have already received a reduced dose of panobinostat due to adverse events. If this is unavoidable, patients should be closely monitored and further dose reduction or discontinuation may be considered as clinically indicated.

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 section CLINICAL PHARMACOLOGY and section WARNINGS AND PRECAUTIONS).

Patients with hepatic impairment

A 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. Patients with mild hepatic impairment should be started on panobinostat at a reduced dose of 15 mg during the first treatment cycle. A dose escalation from 15 mg to 20 mg may be considered based on patient tolerability. Patients with

moderate hepatic impairment should be started on panobinostat at a reduced dose of 10 mg during the first treatment cycle. A dose escalation from 10 mg to 15 mg may be considered based on patient tolerability. Frequency of monitoring of these patients should be increased during treatment with panobinostat, particularly during the dose escalation phase. Panobinostat should not be administered in patients with severe hepatic impairment due to lack of experience and safety data in this population. Adjustment of bortezomib dose should also be considered (see bortezomib prescribing information and Table 6).

Table 6 Recommended starting dose modification for patients with hepatic impairment

Grade of hepatic impairment*	Bilirubin level	SGOT (AST) levels	Modification of panobinostat starting dose	Modification of bortezomib starting dose
Mild	≤1.0 x ULN	>ULN	Reduce panobinostat dose to 15 mg in the first treatment cycle. Consider dose escalation up to 20 mg in subsequent cycles based on patient tolerability.	None
	>1.0 x ULN and ≤1.5 x ULN	Any		
Moderate	>1.5 x ULN and ≤3.0 x ULN	Any	Reduce panobinostat dose to 10 mg in the first treatment cycle. Consider dose escalation up to 15 mg in subsequent cycles based on patient tolerability.	Reduce bortezomib dose to 0.7 mg/m^2 in the first treatment cycle. Consider dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.
SGOT = serum glutamic oxaloacetic transaminase; AST = aspartate aminotransferase ULN = upper limit of the normal range *Based on NCI-CTEP classification				

Pediatric patients

No studies have been performed and there is no relevant use of panobinostat in pediatric patients below the age of 18 in the indication of multiple myeloma (see section CLINICAL PHARMACOLOGY).

Geriatric 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 section CLINICAL 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 section ADVERSE DRUG REACTIONS for more details).

Geriatric 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.

Method of administration

Farydak capsules should be administered orally once daily on scheduled days only, at the same time each day. Capsules should be swallowed whole with water. Farydak can be taken with or without food (see section CLINICAL 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.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

WARNINGS AND PRECAUTIONS

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

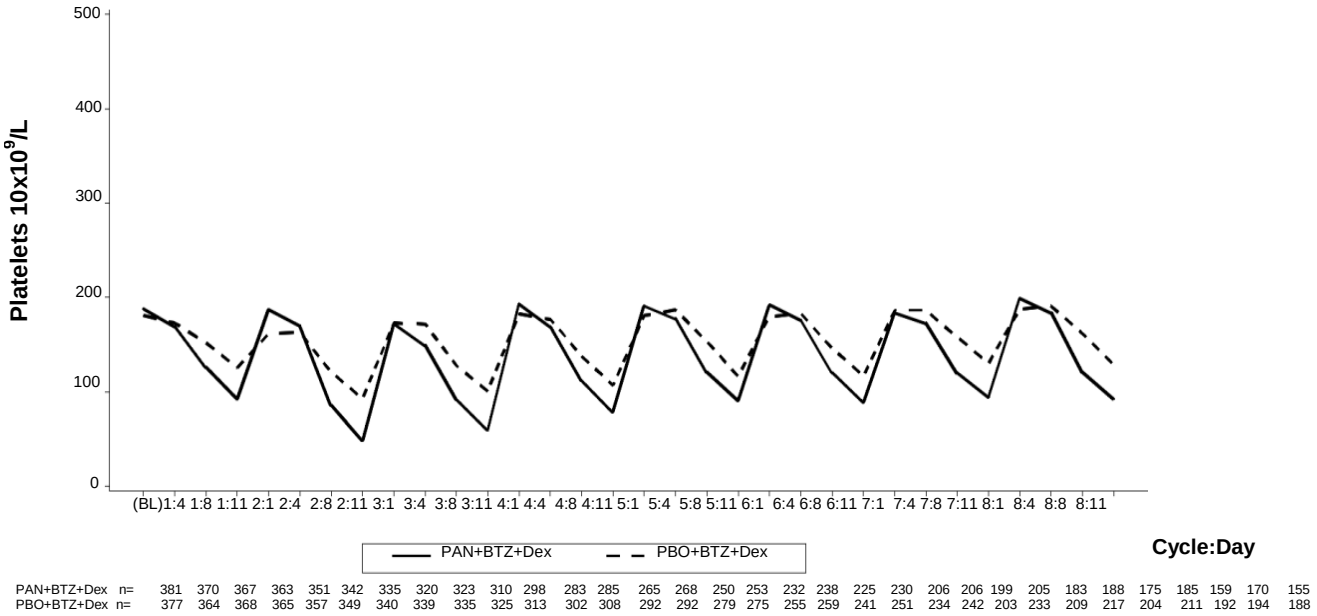
Decrease in blood cell count

Hematologic adverse drug reactions, including severe thrombocytopenia, neutropenia and anemia (CTCAE grade 3 to 4) were reported in patients treated with panobinostat. Therefore, a complete blood count must be performed before initiating therapy with panobinostat and frequently monitored during treatment.

The platelet count should be $\geq 100 \times 10^9$/L and the absolute neutrophil count should be $\geq 1.0 \times 10^9$/L prior to initiation of treatment. The platelet count should be $\geq 100 \times 10^9$/L prior to initiating any cycle of treatment. (see section DOSAGE AND ADMINISTRATION).

In the Phase III study, thrombocytopenia typically recovered to baseline by the start of the next 21-day cycle (Figure 1). The median time to onset was one month and the median time to recovery was 12 days.

Figure 1 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) panobinostat 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 sections DOSAGE AND ADMINISTRATION and ADVERSE DRUG REACTIONS).

Hemorrhage

Hemorrhage has been reported in patients during treatment with panobinostat. CTCAE grade 3 to 4 hemorrhage was reported in 4.2% of patients, including cases of GI and pulmonary hemorrhage with fatal outcomes. Therefore, physicians and patients should be aware of the increased risk of thrombocytopenia and the potential for hemorrhage, 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 panobinostat. 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 section ADVERSE DRUG REACTIONS). 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 section ADVERSE DRUG REACTIONS). Physicians and patients should be aware of the increased risk of infection with panobinostat.

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

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

Gastrointestinal disorders

Severe nausea, diarrhea, constipation, and vomiting, sometimes requiring the use of antiemetic and antidiarrheal medications have been reported in patients treated with panobinostat (see section ADVERSE DRUG REACTIONS). 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 section DOSAGE AND ADMINISTRATION).

Prophylactic anti-emetics (e.g. prochlorperazine) 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, granisetron, ondansetron and tropisetron should be used with caution.

At the first sign of abdominal cramping, loose stools, or onset of diarrhea, it is recommended that the patient be treated with anti-diarrheal medication (e.g. loperamide) 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 diarrhea. Patients should be advised to contact their physician to discuss any laxative use.

Cardiac Toxicities and Electrocardiographic changes

Severe and fatal cardiac ischemic events, as well as severe arrhythmias, and electrocardiogram (ECG) changes occurred in patients receiving panobinostat. Arrhythmias occurred in 12% of patients receiving panobinostat, compared to 5% of patients in the control arm. Cardiac ischemic events occurred in 4% of patients treated with panobinostat compared with 1% of patients in the control arm. Do not initiate panobinostat treatment in patients with history of recent myocardial infarction or unstable angina.

Panobinostat may prolong cardiac ventricular repolarization (QT interval) (see section NON-CLINICAL SAFETY DATA).

No episodes of QTcF prolongation >500 msec have been reported with the dose of 20 mg panobinostat 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 were observed.

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

QTcF should be <480 msec prior to initiation of treatment with panobinostat.

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 DOSAGE AND ADMINISTRATION).

Panobinostat 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 recent myocardial infarction, congestive heart failure and unstable angina or clinically significant bradycardia.

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

Hepatotoxicity

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

Liver function should be monitored prior to treatment and regularly during treatment. If abnormal liver function tests are observed, dose adjustments may be considered and the patient should be followed until values return to normal or pre-treatment levels (see section DOSAGE AND ADMINISTRATION).

Strong CYP3A4 inducers

Strong inducers may reduce the efficacy of panobinostat, therefore the concomitant use of strong CYP3A4 inducers including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin and St. John's Wort (*Hypericum perforatum*), should be avoided (see section INTERACTIONS).

Elderly population

It is recommended to monitor patients over 65 years of age more frequently, especially for thrombocytopenia and gastrointestinal toxicity (see section ADVERSE DRUG REACTIONS).

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 sections ADVERSE DRUG REACTIONS and DOSAGE AND ADMINISTRATION).

Women of childbearing potential

Women of childbearing potential taking panobinostat in combination with bortezomib and dexamethasone must use highly effective contraception for three months after stopping treatment (see sections INTERACTIONS and PREGNANCY, LACTATION, FEMALE AND MALES OF REPRODUCTIVE POTENTIAL, and bortezomib and dexamethasone prescribing information). Women using hormonal contraceptives should additionally use a barrier method of contraception.

Hypothyroidism

Hypothyroidism events were reported in 8 of 381 patients treated with panobinostat + bortezomib + dexamethasone in Study D2308, of whom 2 required treatment. Thyroid and pituitary function should be monitored by measuring hormone levels (e.g. free T4 and TSH) as clinically indicated (see section DOSAGE AND ADMINISTRATION).

ADVERSE DRUG REACTIONS

Summary of the safety profile

The safety data below reflect patient exposure to panobinostat from the phase III clinical study, in which 758 patients with relapsed multiple myeloma received panobinostat in combination with bortezomib and dexamethasone or placebo in combination with bortezomib and dexamethasone. Patients were 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.

The most common non-hematologic adverse reactions were diarrhea, fatigue, nausea, and vomiting.

Treatment emergent hematologic toxicities included thrombocytopenia, anemia, neutropenia and lymphopenia (see Table 8 for laboratory abnormalities).

QTcF >480 and <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 adverse events, regardless of causality was observed in 36.2% of patients. The most common ADRs leading to treatment discontinuation were: diarrhea (4.5%), asthenia, fatigue (2.9% each), and pneumonia (1.3%).

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 hemorrhage.

Adverse drug reactions from the phase III trial are shown in Table 7. 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 7 Adverse reactions observed in at least ≥ 10% of multiple myeloma patients in the phase III trial[1]

Primary System Organ Class Preferred Term	Panobinostat, BTZ[2], Dex[3] N=381 (%) all grades	Placebo, BTZ[2], Dex[3] N=377(%) all grades	Panobinostat, BTZ[2], Dex[3] N=381(%) grade 3-4	Placebo, BTZ[2], Dex[3] N=377 (%) grade 3-4	Frequency Category (overall)
Infections and infestations					
Upper respiratory tract infection	18	15	2	2	Very common
Pneumonia	17	13	13	10	Very common
Metabolism and nutrition disorders					
Decreased appetite	28	13	3	1	Very common

Psychiatric disorders					
Insomnia	19	16	0.0	<1	Very common
Nervous system disorders					
Dizziness	19	16	3	2	Very common
Headache	14	11	<1	<1	Very common
Vascular disorders					
Hypotension	14	9	3	1	Very common
Respiratory, thoracic and mediastinal disorders					
Cough	21	19	1.0	0.0	Very common
Dyspnea	15	12	2	2	Very common
Gastrointestinal disorders					
Diarrhea	68	42	26	8	Very common
Nausea	36	21	6	<1	Very common
Vomiting	26	13	7	1	Very common
Abdominal pain	13	11	2	<1	Very common
Dyspepsia	12	11	<1	<1	Very common
General disorders and administration site conditions					
Fatigue	41	29	17	9	Very common
Edema peripheral	29	19	2	<1	Very common
Pyrexia	26	15	1	2	Very common
Asthenia	22	15	9	4	Very common
Investigations					
Weight decreased	12	5	2	<1	Very common

[1] ADRs with a difference in frequency <1% between active arm and PBO arm are not listed (e.g. peripheral neuropathy, commonly reported with BTZ treatment)

[2] BTZ = bortezomib

[3] Dex = dexamethasone

Laboratory abnormalities

Clinically relevant or severe abnormalities of routine hematological or biochemical laboratory values are presented in Table 8.

Table 8 Laboratory abnormalities 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)
Hematological parameters					
Thrombocytopenia	98	84	67	31	Very common
Anemia	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
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

Other notable ADRs which occurred with a frequency less than 10% in the phase III trial

Infections and infestations: *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.

Endocrine disorders: *Common:* hypothyroidism.

Metabolism and nutrition disorders: *Common:* hyperglycemia, dehydration, hypoalbuminemia, fluid retention, hyperuricemia, hypocalcemia, hypomagnesemia.

Nervous system disorders: *Common:* hemorrhage intracranial, syncope, tremor, dysgeusia.

Eye disorders: *Common:* conjunctival hemorrhage.

Cardiac disorders: *Common:* bradycardia, atrial fibrillation, sinus tachycardia, tachycardia, palpitations. *Uncommon:* myocardial infarction.

Vascular disorders: *Common:* hypertension, hematoma, orthostatic hypotension.
Uncommon: shock hemorrhagic.

Respiratory, thoracic and mediastinal disorders: *Common:* respiratory failure, rales, wheezing, epistaxis. *Uncommon:* pulmonary hemorrhage, hemoptysis.

Gastrointestinal disorders: *Common:* gastrointestinal hemorrhage, hematochezia, gastritis, cheilitis, abdominal distension, dry mouth, flatulence. *Uncommon:* colitis, hematemesis, gastrointestinal pain.

Hepatobiliary disorders: *Common:* hepatic function abnormal.

Skin and subcutaneous disorders: *Common:* skin lesions, rash, erythema. *Uncommon:* petechie.

Musculoskeletal and connective tissue disorders: *Common:* joint swelling.

Renal and urinary disorders: *Common:* renal failure, hematuria, urinary incontinence.

General disorders and administration site conditions: *Common:* chills, malaise.

Investigations: *Common:* blood urea increased, glomerular filtration rate decreased, blood alkaline phosphatase increased, electrocardiogram QT prolonged.

Description of selected Adverse Drug Reactions

Gastrointestinal

GI toxicities, primarily diarrhea, nausea and vomiting, are among the most frequently reported adverse reactions. However, treatment discontinuation due to these events were reported in a relatively small proportion of patients with diarrhea at 4.5%, nausea and vomiting at 0.5% each. Patients should be advised to contact their physicians when severe GI toxicity occurs and dose adjustment or discontinuation may be required.

Thrombocytopenia

Due to the nature of multiple myeloma and the known hemato-toxicity for panobinostat and its combination agent bortezomib, thrombocytopenia, often severe, has been frequently observed. CTCAE grade 3-4 thrombocytopenia occurred in 256 patients, with a median onset time of 1 month. However, thrombocytopenia is reversible (median time to recovery of 12 days) and can usually be effectively managed by dose adjustment and interruption with or without platelet transfusion. 33.3% patients in the panobinostat + bortezomib + dexamethasone arm and 10.3% patients in the placebo + bortezomib + dexamethasone arm received platelet transfusions during treatment. Thrombocytopenia seldom leads to treatment discontinuation (1.6% of patients). Most of patients with thrombocytopenia did not experience hemorrhage. There were 20.7% patients experienced hemorrhage, most frequently epistaxis (4.7%), hematoma (2.6%), and conjunctival hemorrhage (2.1%). CTCAE grade 3-4 hemorrhage was reported in 4.2% of the patients, mostly commonly involving gastrointestinal hemorrhage. Five patients (1.3%) died of events associated with haemorrhage. Amongst the patients who died of haemorrhage, one patient had thrombocytopenia grade 4, three patients had thrpmbocytopenia grade 3 and 1 patient had thrombocytopenia grade 1.

Neutropenia

Neutropenia was frequently reported by laboratory findings during study (all grades: 75%). 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 3to 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.

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.

Infections

Relapsed or refractory multiple myeloma patients are at risk of infections. Potential contributing factors may include prior history of chemotherapy, stem cell transplant, the nature of the disease and neutropenia or lymphopenia associated with panobinostat treatment. The most frequently reported infections include upper respiratory tract infection, pneumonia

and nasopharyngitis. Fatality with pneumonia or sepsis was reported. Treatment discontinuation due to infections was reported for 5% of the patients.

QT prolongation and ECG abnormalities

QTc prolongation was observed, mostly mild in degree: QTcF interval >450 ms and ≤480 ms was reported in 10.8% of patients, with maximum increase from baseline >30 ms and ≤60 ms in 14.5% of patients. No patients reported > 500 ms QTcF. ECG (electrocardiogram) abnormalities have been reported in patients treated with panobinostat + bortezomib + dexamethasone, mainly involving ST-T depression (21.7%) and T wave changes (39.6%). Regardless of events chronology, syncope was reported in 9% of patients with ST-T depression and 7.2% of patients with T wave change and 4.9% of patients with neither of these ECG abnormalities. Likewise ischaemic heart disease (including myocardial infarction and ischaemia) were reported in 4.5% of patients with ST-T depression and 4.8% of patients with T wave change and 2.7% of patients with neither of these ECG abnormalities.

Special populations

Elderly patients

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 years of age.

Adverse reactions leading to permanent discontinuation occurred in 30%, 44% and 47% of patients aged <65 years, 65 to 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%), anemia (16%, 17% and 29%), diarrhea (21%, 27% and 47%), and fatigue (18%, 28% and 47%).

INTERACTIONS

Panobinostat metabolism is primarily through non-CYP and CYP mediated routes. Approximately 40% of panobinostat is metabolized through CYP3A4. Metabolism via CYP2D6 and 2C19 were minimally involved *in vitro*. Therefore, medicinal products which can influence the CYP3A4 enzyme activity may alter the pharmacokinetics of panobinostat. Panobinostat is a Pgp substrate.

In vitro, panobinostat is a competitive inhibitor of CYP2D6 and a weak time-dependent CYP3A4 inhibitor.

Agents that may increase panobinostat plasma concentrations

Co-administration of a single 20 mg panobinostat dose with ketoconazole, a strong CYP3A inhibitor, increased the C_{max} and AUC of panobinostat by 1.6- and 1.8 respectively, compared to when panobinostat was given alone.

The dose of panabinostat should be reduced in patients who take concomitant medicinal products which are strong CYP3A and/or Pgp inhibitors, including but not limited to ketoconazole, itraconazole, voriconazole, ritonavir, saquinavir, telithromycin, posaconazole, and nefazodone (see section DOSAGE AND ADMINISTRATION).

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

Agents that are predicted to decrease panobinostat concentrations

Panobinostat fraction metabolized through CYP3A4 is approximately 40%. In clinical studies in multiple myeloma, the exposure of panobinostat was decreased by 20to 50% by the concomitant use of dexamethasone which is a dose-dependent mild/moderate CYP3A4 inducer. Furthermore, in-silico data showed that the systemic exposure of panobinostat may be decreased by 70% in the presence of strong inducers of CYP3A4. Therefore, the concomitant use of strong CYP3A4 inducers should be avoided.

Agents whose plasma concentrations may be increased by panobinostat

Panobinostat increased the C_{max} and the AUC of dextromethorphan (a sensitive substrate of CYP2D6) by 1.8- and 1.6-fold, respectively. Avoid co-administration of sensitive CYP2D6 substrates (including but not limited to atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine and venlafaxine) with panobinostat or CYP2D6 substrates that have a narrow therapeutic index (including, but not limited to thioridazine and pimozide). If concomitant use of CYP2D6 substrates is unavoidable, monitor patients frequently for adverse reactions.

Agents whose plasma exposure can be decreased by panobinostat

Hormonal contraceptives
It is currently unknown whether panobinostat may reduce the effectiveness of hormonal contraceptives. In addition, when panobinostat is administered together with dexamethasone, which is known to be a weak to moderate inducer of CYP3A4 as well as other enzymes and transporters, the risk for reduced efficacy of contraceptives needs to be considered. Women using hormonal contraceptives should additionally use a barrier method of contraception.

No data is available that can be used to exclude the risk that panobinostat could be a weak inducer of the enzyme CYP3A4 in the gastrointestinal tract. This could potentially lead to slightly decreased exposure to sensitive CYP3A4 substrates.

Anticipated pharmacodynamic interactions

Prolongation of 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, granisetron, ondansetron and tropisetron should be used with caution (see section WARNINGS AND PRECAUTIONS).

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary:

Panobinostat can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. The patient should be advised of the

risk to a fetus, if panobinostat is used during pregnancy or if the patient becomes pregnant while taking this drug.

Reproductive toxicity studies in rats and rabbits have demonstrated panobinostat induced embryo-fetal toxicity and teratogenicity. Increased incidences of malformations were observed in rats and rabbits following prenatal exposure to panobinostat at concentrations at or lower than the exposure in humans at the highest recommended dose (20 mg).

Animal data:

In embryo-fetal development studies, panobinostat was administered orally 3 times per week during the period of organogenesis to pregnant rats (30, 100, and 300 mg/kg) and rabbits (10, 40, and 80 mg/kg). In rats, maternal toxicity including death was observed at doses greater than or equal to 100 mg/kg/day. Embryo-fetal toxicities occurred at 30 mg/kg (the only dose with live fetuses) and consisted of fetal malformations and anomalies, such as cleft palate, short tail, extra presacral vertebrae, and extra ribs. The dose of 30 mg/kg resulted in exposures (AUCs) approximately 3-fold the human exposure at the human dose of 20 mg. In rabbits, maternal toxicity including death was observed at doses greater than or equal to 80 mg/kg. Increased pre- and/or post-implantation loss occurred at all doses tested. Embryo-fetal toxicities included decreased fetal weights at doses greater than or equal to 40 mg/kg and malformations (absent digits, cardiac interventricular septal defects, aortic arch interruption, missing gallbladder, and irregular ossification of skull) at 80 mg/kg. The dose of 40 mg/kg in rabbits results in systemic exposure approximately 4-fold the human exposure and the dose of 80 mg/kg results in exposure 7-fold the human exposure, at the human dose of 20 mg.

Lactation

It is unknown whether panobinostat is excreted in human milk. There are no data on the effects of panobinostat on the breastfed child or the effects of panobinostat on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from panobinostat, decide whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Females and males of reproductive potential

Pregnancy testing:

Sexually-active females of reproductive potential should have a pregnancy test prior to the initiation of treatment with panobinostat and intermittently during treatment with panobinostat.

Contraception:

Females of reproductive potential should be advised that animal studies have shown panobinostat to be harmful to the developing fetus. Sexually-active females of reproductive potential should use effective contraception (methods that result in less than 1 % pregnancy rates) when using panobinostat during treatment and for 3 months after stopping treatment with panobinostat.

Sexually-active males taking panobinostat should use a condom during intercourse with females of reproductive potential or pregnant women and for 6 months after stopping treatment with panobinostat to avoid conception or embryo-fetal harm. Female partners of sexually active men should also use an effective contraception (methods that result in less than 1 % pregnancy rates) during treatment and for 6 months after their male partner has stopped taking panobinostat.

Infertility

Based on non-clinical findings, male fertility may be compromised by treatment with panobinostat (see section NON-CLINICAL SAFETY DATA).

OVERDOSAGE

Limited experience with overdose has been reported during clinical trials. Adverse reactions observed were consistent with the safety profile with events primarily involving hematologic and GI disorders such as thrombocytopenia, pancytopenia, diarrhea, 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.

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group: Other antineoplastic agents

Mechanism of action (MOA)

Panobinostat, a hydroxamic acid derivative, is a potent class I/II pan-deacetylase inhibitor (DACi) with anti-tumor activity. DACi are a novel class of anticancer agents that target epigenetic changes via gene expression modulation. HDACs catalyze the removal of acetyl groups from the lysine residues of histones and some non-histone proteins. Inhibition of HDAC activity results in increased acetylation of histone proteins, an epigenetic alteration that results in a relaxing of chromatin, leading to transcriptional activation. Panobinostat has been shown to inhibit the proliferation of a variety of tumor cell lines at low nanomolar concentrations *in vitro.* In addition, activation of the p21 promoter, a key mediator of G1 arrest and differentiation, was triggered with panobinostat exposure. Treatment of tumor cells with panobinostat resulted in a dose dependent increase acetylation of histones H3 and H4, including at low nanomolar concentrations, demonstrating robust target inhibition. *In vitro* experiments suggest that panobinostat selectively targets tumor cells, and provides a basis for a potentially favorable therapeutic window during anticancer therapy. Furthermore, in *in vivo* efficacy studies where decrease in tumor burden following panobinostat treatment was observed tumor tissues excised from mice xenografts exhibited increased levels of acetylated histones. These results demonstrated that the antitumor activity of panobinostat was accompanied by inhibition of histone deacetylases *in vivo*.

Pharmacodynamics (PD)

Panobinostat deacetylates a broad range of deacetylase enzymes including histone proteins as well as several non-histone proteins involved in oncogenesis (e.g. transcription factors p53 and HIF-1alpha, the cytoskeletal factor alpha-tubulin, and the protein chaperone HSP90). Histones are implicated in epigenetic modifications that could cause cancer. Non-histone proteins regulated by DACs have been shown to modulate cancer cell growth and survival pathways. The non-histone proteins may be as important as histones as targets in the treatment of cancers.

The downstream effects of DACi by panobinostat on several key proteins may result in an increase in tumor suppressor gene activity (p21, p27); or increase in microtubule polymerization which is associated with abnormal mitosis, decreased cell survival, motility and invasion. In addition, DACi inhibits HSP90 deacetylase, leading to increased acetylation of HSP90, inhibition of chaperone activity and increased degradation of associated onco-

proteins. In summary, panobinostat is a pan-DAC inhibitor which targets several hallmarks of cancer (e.g., P53, HIF-1alpha, HSP90, alpha-tubulin, and histones). DAC inhibition may ultimately result in cell-cycle arrest, apoptosis and decreases in cell motility and invasion, angiogenesis, and cell proliferation and survival.

Pharmacokinetics (PK)

Absorption

Panobinostat is rapidly absorbed with T_{max} reached within 2 hours of oral administration in patients with advanced cancer. The absolute oral bioavailability of panobinostat was approximately 21%. After oral administration, panobinostat pharmacokinetics appear to be linear in the dose range 10-30 mg, but AUC increases less than proportionally with dose at higher doses.

Overall panobinostat exposure and inter-patient variability remained unchanged with or without food, whereas C_{max} was reduced by <45% and T_{max} 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 regardless of food in cancer patients.

Distribution

Panobinostat is moderately (approximately 89%) bound to human plasma proteins. Its fraction in the erythrocyte is 0.60 *in vitro,* independent of the concentration. Protein binding is considered to have little effect on the availability of panobinostat for target binding, and displacement of highly protein-bound compounds by panobinostat is unlikely.

Biotransformation / 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. The parent drug is deemed to be responsible for the overall pharmacological activity of panobinostat.

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 feces. Unchanged panobinostat accounted for <2.5% of the dose in urine and <3.5% of the dose in feces. The remainders are metabolites. Apparent panobinostat renal clearance (CL_R/F) was found to range from 2.4 to 5.5 L/h. Panobinostat has a terminal elimination half-life of approximately 37 hours based on final parameters estimate in the population PK analysis.

Special populations

Pediatric patients

Panobinostat was not evaluated in Multiple myeloma 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. Mild and moderate hepatic impairment per NCI-CTEP classification increased panobinostat plasma exposure by 43% and 105%, respectively, with no apparent impact on patients' AE profiles. No PK data for severe hepatic impaired patients are available (see sections DOSAGE AND ADMINISTRATION and WARNINGS 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 tumors 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 panobinostat (see section DOSAGE AND ADMINISTRATION).

CLINICAL STUDIES

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 randomized, double-blind, placebo-controlled, multicenter phase III study in patients with relapsed or relapsed-and-refractory multiple myeloma who had received 1 to 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 Tables 1 and 2).

A total of 768 patients were randomized in a 1:1 ratio to panobinostat, bortezomib and dexamethasone (n=387) or placebo, bortezomib and 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 to 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 to 1 in 93% of patients. The median number of prior therapies is 1.0. 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 median duration of follow-up was 28.75 months in the panobinostat, bortezomib and dexamethasone arm and 29.04 months in the placebo, bortezomib and 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. In the overall patient population PFS based on the full analysis set (FAS), was statistically significantly different between the treatment arms (stratified Log-rank test p<0.0001, with an estimated 37% risk reduction in the panobinostat, bortezomib and dexamethasone arm compared to the placebo, bortezomib and dexamethasone arm (Hazard ratio: 0.63 (95% CI: 0.52, 0.76)). The median PFS (95% CI) was 12.0 months (10.3 to 12.9) and 8.1 months (7. 6 to 9.2), respectively.

Overall survival (OS) was the key secondary endpoint. OS was not statistically significantly different between the two treatment groups. The median OS was 40.3 months in the panobinostat + bortezomib + dexamethasone arm and 35.8 months in the placebo + bortezomib + dexamethasone arm (Hazard ratio: 0.94 (95% CI: 0.78, 1.14)).

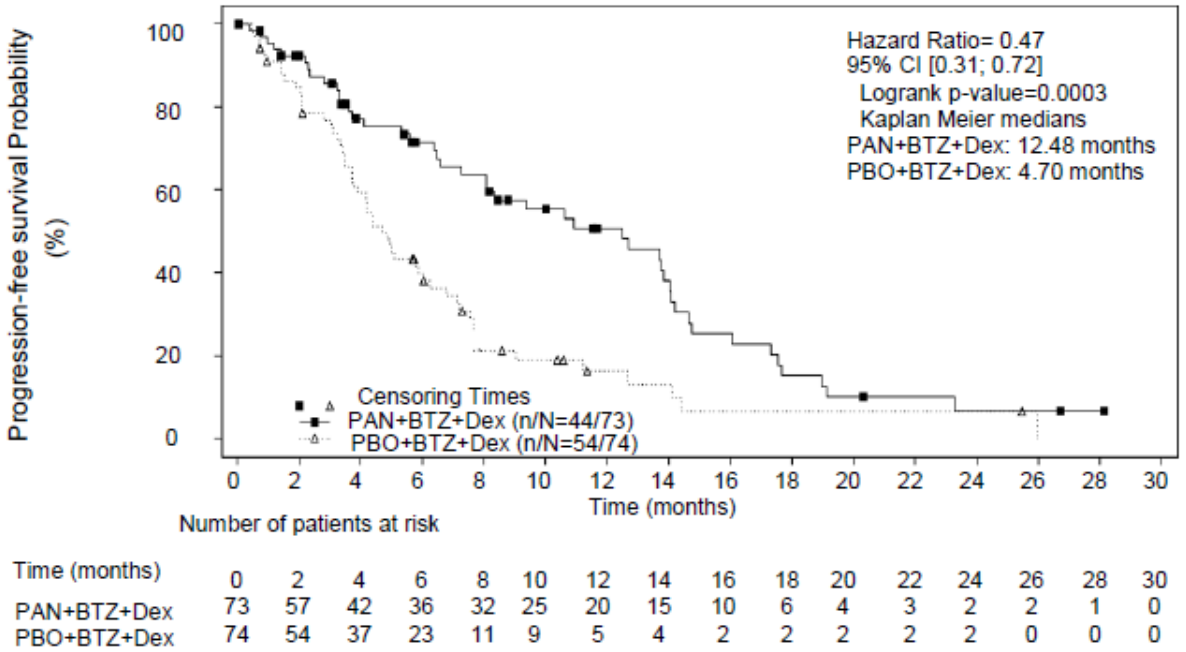
Out of the pre-specified subgroup of patients with prior treatment with bortezomib and an immunomodulatory agent (N=193), 76% of patients had received at least two prior regimens. In this subset of patients (N=147), the median duration of treatment was 4.5 months in the panobinostat + bortezomib + dexamethasone arm and 4.8 months in the placebo + bortezomib + dexamethasone arm. The median PFS (95% CI) was 12.5 months (7.26, 14.03) in the panobinostat + bortezomib + dexamethasone arm and 4.7 months (3.71, 6.05) in the placebo + bortezomib + and dexamethasone arm [HR: 0.47 (0.31, 0.72)]. These patients had a median of 3 prior therapies. Efficacy results are summarised in Table 9 and the Kaplan-Meier curves for PFS are provided in Figure 2.

Table 9: Progression-free survival in patients who received at least two prior regimens including bortezomib and an immunomodulating agent

	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)	

[1] Hazard ratio obtained from stratified Cox model

Figure 2: 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



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

In the subgroup of patients who had received at least two prior regimens including bortezomib and an immunomodulatory agent (n=147), the overall response rate using modified EBMT criteria was 59% in the panobinostat + bortezomib + dexamethasone arm and 39% in the placebo + bortezomib + dexamethasone arm. Response rates are summarised in Table 10.

Table 10: Response rates in patients with multiple myeloma who received at least two prior regimens including bortezomib and an immunomodulatory agent

	Farydak bortezomib and dexamethasone N=73	**Placebo bortezomib and dexamethasone N=74**
Overall response [95% CI]	43 (59%) (46.8, 70.3)	29 (39%) (28, 51.2)
Complete response	6 (8%)	0
Near complete response	10 (14%)	6 (8%)
Partial response	27 (37%)	23 (31%)

Clinical efficacy in patients with bortezomib refractory Multiple Myeloma (Study DUS71)

Study DUS71 was a phase II, two stage, single arm, open label, multi-center study of oral panobinostat (20 mg) in combination with iv bortezomib (1.3 mg/m^2) and oral dexamethasone (20 mg) in 55 patients with relapsed and refractory multiple myeloma, who were BTZ-refractory and had received at least 2 prior lines of therapy. Patients had to be exposed to an immunomodulatory drug (IMiD) (lenalidomide or thalidomide). Refractoriness to bortezomib was defined as disease progression on or within 60 days of the last bortezomib containing line of therapy.

Primary endpoint of the study was to assess overall response rate (ORR) after 8 cycles of therapy as per modified by European Bone Marrow Transplant (EBMT) organization criteria.

Patients were heavily pre-treated and had received multiple prior regimens (median 4; range: 2 to 11). All 55 patients were previously treated with bortezomib, and at least one IMiD (lenolidomide: 98.2%, thalidomide: 69.1%). The majority of patients had received prior transplant (63.6%).

The median duration of exposure to study treatment was 4.6 months (range: 0.1 to 24.1 months). Patients achieved an ORR (≥ PR (partial response)) of 34.5% and 52.7% (≥ MR (minimal response)). The median time to response was 1.4 months and the median duration of response was 6.0 months. The median OS was 17.5 months.

NON-CLINICAL SAFETY DATA

Safety pharmacology

Safety pharmacology studies indicate that panobinostat is unlikely to interfere with vital functions of the respiratory and CNS systems. *In vitro* electrophysiology data and *in vivo* telemetry studies in dogs showed consistent signals for QT prolongation.

Carcinogenesis and Mutagenesis

Carcinogenicity studies have not been performed with panobinostat. Panobinostat has demonstrated mutagenic potential in the Ames assay, endo-reduplication effects in human peripheral blood lymphocytes *in vitro*, and DNA damage in an *in vivo* COMET study in mouse lymphoma L5178Y cells, that are attributed to the pharmacological mode of action.

Pregnancy

Based on animal data, the likelihood of panobinostat increasing the risk of fetal death and developmental skeletal abnormalities is predicted to be high. Reproductive studies performed in pregnant rats with oral doses showed embryo-fetal-lethality, increases in skeletal variations and anomalies (extra vertebrae, extra ribs, and increases in minor skeletal variations) at doses that also produced maternal toxicity and decreases in fetal body weight. The no observed adverse effect levels (NOAELs) in pregnant rats was 10 mg/kg/day.

Reproductive studies were performed in pregnant rats and rabbits at oral doses up to 38 times the recommended human dose. 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. Decreases in fetal body weight and maternal toxicity were also observed. The NOAELs for these findings in pregnant rabbits was 10 mg/kg/day.

The effects of panobinostat on labor and post-natal growth and maturation were not evaluated in animal studies.

Fertility

In an oral fertility study conducted in rats, 10, 30 and 100 mg/kg doses of panobinostat were administered to females 3 times weekly (days 1, 3 and 5) for 2 weeks prior to mating, then during the mating period, and on gestation days 0, 3 and 6. An increase in early resorptions in female rats was observed at doses ≥30 mg/kg. Maternal food consumption decrease and decreased body weight also occurred at these doses and may have contributed to the effect. The no effect level for maternal fertility was 10 mg/kg. In the same study effects on male fertility were not seen when panobinostat was administered orally for 4 weeks (same dose and regimen). However, prostatic atrophy accompanied by reduced secretory granules, and testicular degeneration, oligospermia and increased epididymal debris were observed in 4-

and 13-week repeated dose oral toxicity studies in dogs given doses of 1.5 mg/kg and 1.5 to1.0 mg/kg. These effects were not completely reversible following a 4-week recovery period. Therefore, males should also be advised of possible risks to fertility.

Repeated dose toxicity studies

The primary target organs of toxicity following administration of panobinostat in rat and dog were identified as the erythropoietic, myelopoietic and lymphatic systems. Gastrointestinal tract changes consisting of diarrhea, dilation of small intestinal crypts with necrotic debris and inflammatory cells, and single cell necrosis of epithelial cells of the cardiac region of the stomach were observed in dogs at doses ≥1.5 mg/kg and ulcerative lesions of the intestinal tract were observed following consecutive daily dosing in embryo-fetal development studies in rat at doses ≥100 mg/kg/day and rabbit at doses ≥80 mg/kg/day.

Thyroid hormone changes were present in 13-week oral studies in rat and dog and included decreases in triodothyronine (T_3) at doses ≥10 mg/kg in the rat and at a dose of 1.5→1.0 mg/kg in the dog and decreases in tetraiodothyronine (T_4) (males) and thyroid stimulating hormone (TSH) (females) in the rat at 100 mg/kg.

Histopathological changes observed in animal studies

Histopathological and functional changes of the thyroid were observed in rats and dogs included decreases in follicular colloid and epithelial vacuolation in 4-week oral studies in dogs at doses ≥0.15 mg/kg, and dose dependent increases in thyroid follicular hypertrophy in rats after 26 weeks of treatment doses ≥10 mg/kg. A benign thyroid follicular cell adenoma was also seen in one rat in the 26-week study at 75 mg/kg. The lack of significant and sustained increases in TSH combined with the cytostatic/cytotoxic effects of panobinostat in the thyroid suggests that the adenoma was unlikely to have been due to panobinostat. Hyperostosis of the femoral cavity was also observed in the rat at 100 mg/kg.

STORAGE

Special precautions for storage

See folding box.

Do not store above 30°C. Protect from moisture.

Farydak should not be used after the date marked “EXP” on the pack.

Farydak must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

No special requirements

Pack size:

PVC/PCTFE/Alu blister containing 6 capsules.

Packs containing 6, 12 or 24 capsules.

Not all presentations may be available locally

INFORMATION FOR PATIENTS

Compliance card

<table>
<tr>
<td rowspan="9">Farydak (panobinostat) is administered by mouth on days 1, 3, 5, 8, 10, and 12 of a 21-day cycle, in combination with bortezomib and dexamethasone. Take all of your medicines exactly as prescribed by your doctor.

Instructions for using the table on the right:
Under Weeks 1 and 2, fill in the dates of your treatment days.</td>
<th>WEEK 1</th>
<th>WEEK 2</th>
<th>WEEK 3</th>
</tr>
<tr><td>Day 1</td><td>Day 8</td><td rowspan="8">Rest period.
Do not take Farydak.</td></tr>
<tr><td>Day 2</td><td>Day 9</td></tr>
<tr><td>Day 3</td><td>Day 10</td></tr>
<tr><td>Day 4</td><td>Day 11</td></tr>
<tr><td>Day 5</td><td>Day 12</td></tr>
<tr><td>Day 6</td><td>Day 13</td></tr>
<tr><td>Day 7</td><td>Day 14</td></tr>
</table>

Manufacturer:

See folding box.

International Package Leaflet

Information issued: Oct 2015.SIN

® = registered trademark

Novartis Pharma AG, Basel, Switzerland