1. NAME OF THE MEDICINAL PRODUCT

Farydak 10 mg hard capsules
Farydak 15 mg hard capsules
Farydak 20 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Farydak 10 mg hard capsules

Each hard capsule contains panobinostat lactate anhydrous equivalent to 10 mg panobinostat.

Farydak 15 mg hard capsules

Each hard capsule contains panobinostat lactate anhydrous equivalent to 15 mg panobinostat.

Farydak 20 mg hard capsules

Each hard capsule contains panobinostat lactate anhydrous equivalent to 20 mg panobinostat.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

Farydak 10 mg hard capsules

Light green opaque hard gelatin capsule (15.6–16.2 mm) containing white to almost white powder, with radial marking “LBH 10 mg” in black ink on cap and two radial bands in black ink on body.

Farydak 15 mg hard capsules

Orange opaque hard gelatin capsule (19.1–19.7 mm) containing white to almost white powder, with radial marking “LBH 15 mg” in black ink on cap and two radial bands in black ink on body.

Farydak 20 mg hard capsules

Red opaque hard gelatin capsule (19.1–19.7 mm) containing white to almost white powder, with radial marking “LBH 20 mg” in black ink on cap and two radial bands in black ink on body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 two prior regimens including bortezomib and an immunomodulatory agent.

4.2 Posology and method of administration

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

Posology

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-day 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).

Panobinostat is administered in combination with bortezomib and dexamethasone, as shown in Tables 1 and 2. The bortezomib and dexamethasone prescribing information should be consulted prior to the start of the combination treatment to assess whether a dose reduction is required.

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.

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 4.4). Prior to initiating any cycle of therapy with panobinostat in combination with bortezomib and dexamethasone, platelet count should be at least ≥100 x 10^9/l (see section 4.4). 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 4.4). 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 below section on dose adjustments and section 4.4).

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 4.4).

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 4.4).

Thyroid function tests
Mild hypothyroidism was reported in patients treated with panobinostat + bortezomib + dexamethasone in Study D2308; some patients required treatment (see section 4.4). Thyroid and pituitary function should be monitored by measuring hormone levels (e.g. free T4 and TSH) as clinically indicated.

Dose adjustments
Modification of the treatment dose and/or schedule may be required based on individual tolerability. Clinical judgement on how to continue the treatment should be exercised when a patient experiences an adverse drug reaction.

If a dose reduction is required, the dose of panobinostat should be reduced by decrements of 5 mg (i.e. from 20 mg to 15 mg or from 15 mg to 10 mg). The dose should not be reduced below 10 mg and the same treatment schedule (3-week treatment cycle) should be kept.

Thrombocytopenia
Platelet counts should be monitored prior to each dose of bortezomib (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, panobinostat may need to be temporarily withheld and the subsequent dose may need to be reduced (see Table 3). In patients with platelet count <50 x 10^9/l (complicated by bleeding) or <25 x 10^9/l, Farydak therapy should be withheld and resumed at a reduced dose upon recovery to platelet count ≥50 x 10^9/l. Platelet counts should be monitored at least twice a week until ≥50 x 10^9/l. Platelet transfusions may be required, if clinically indicated (see section 4.4). Discontinuation of treatment may be considered if thrombocytopenia does not improve despite the treatment modifications described below and/or the patient requires repeated platelet transfusions. Additionally, dose adjustment of bortezomib may be considered (see bortezomib SmPC and Table 3).

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 (≥50 x 10^9/l)**	**Modification of bortezomib starting dose**	**Bortezomib dose on recovery to grade 2 thrombocytopenia (≥50 x 10^9/l)**	
				1 dose omitted	**More than 1 dose omitted**
Grade 3 Platelets <50 x 10^9/l with bleeding	Omit dose	Resume at reduced dose	Omit dose	Resume at same dose	Resume at reduced dose
Grade 4 Platelets <25 x 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 diarrhoea 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-diarrhoeal medicinal product	Omit dose	Resume at the same dose	Omit dose	Resume at reduced dose or change to once weekly
	Grade 3 despite anti-diarrhoeal 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-diarrhoeal medicinal product	Permanently discontinue		Permanently discontinue	

At the first sign of abdominal cramping, loose stools or onset of diarrhoea, it is recommended that the patient be treated with an anti-diarrhoeal medicinal product (e.g. loperamide).

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.

Prophylactic anti-emetics should be administered at the discretion of the physician and in accordance with local medical practice (see section 4.4).

Neutropenia
Neutropenia may require temporary or permanent dose reduction. Instructions for dose interruptions and reductions for panobinostat 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 the event 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 granulocyte colony stimulating factor therapy according to local medical practice and treatment guidelines, and/or in the

event of severe secondary infections.

QTc prolongation
In the event of long QT interval prior to initiation of panobinostat (QTcF ≥480 msec at baseline), the start of treatment should be delayed until pre-dose average QTcF has returned to <480 msec. In addition any abnormal serum potassium, magnesium or phosphorus values should be corrected prior to initiation of Farydak therapy (see section 4.4). In the event 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, Farydak therapy should be permanently discontinued.

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

- CTC grade 2 toxicity recurrence or CTC grades 3 and 4 - omit the dose until recovery to CTC grade ≤1 and resume treatment at a reduced dose.
- CTC grade 3 or 4 toxicity recurrence - a further dose reduction may be considered once the adverse reaction has resolved to CTC grade ≤1.

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 5.2).

Patients with hepatic impairment
A clinical study in cancer patients with impaired hepatic function showed 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 SmPC 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				

Elderly population
Patients over 65 years of age had a higher frequency of selected adverse reactions and of discontinuation of treatment because of adverse reactions. It is recommended to monitor patients over 65 years of age more frequently, especially for thrombocytopenia and gastrointestinal toxicity (see sections 4.4 and 4.8).

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.

Paediatric population
There is no relevant use of panobinostat in paediatric patients below the age of 18 years in the indication multiple myeloma (see section 5.2).

Strong CYP3A4 inhibitors
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, the dose of panobinostat should be reduced to 10 mg (see section 4.5). 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 reactions. If this is unavoidable, patients should be closely monitored and further dose reduction or discontinuation may be considered as clinically indicated (see section 4.5).

Method of administration

Farydak should be administered orally once daily on scheduled days only, at the same time each day. The capsules should be swallowed whole with water, with or without food (see section 5.2), and they 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

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

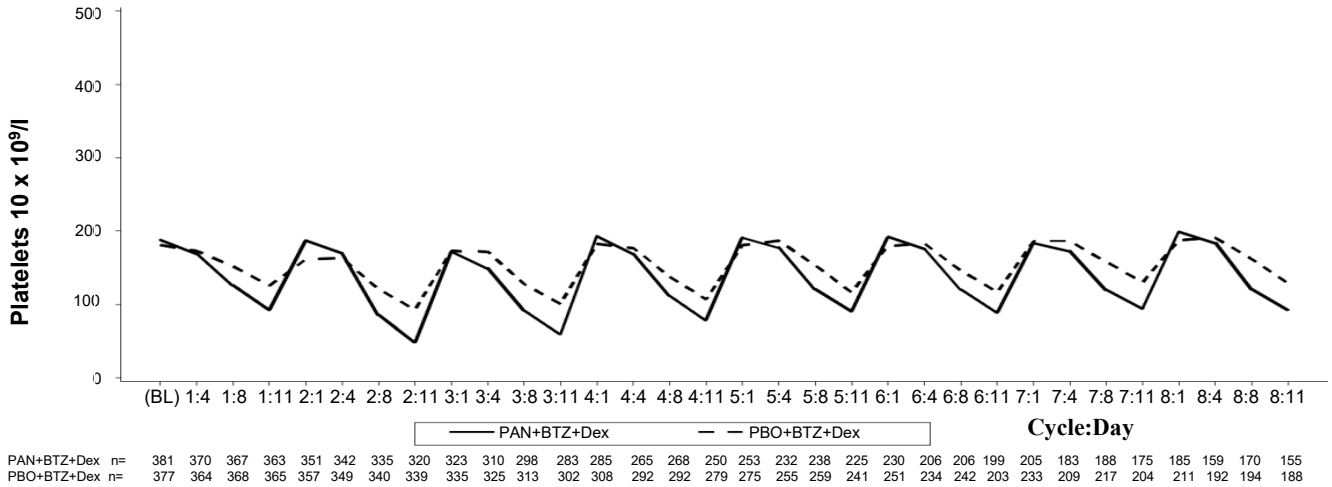
Decrease in blood cell count

Haematological adverse drug reactions, including severe thrombocytopenia, neutropenia and anaemia (CTC grade 3 to 4) were reported in patients treated with panobinostat. Therefore a complete blood count must be performed before initiating therapy with panobinostat, with frequent monitoring during treatment (in particular before each injection of bortezomib as per bortezomib SmPC).

The platelet count should be $\geq 100 \times 10^9$/l and the absolute neutrophil count $\geq 1.0 \times 10^9$/l prior to initiation of treatment. Platelet count should be $\geq 100 \times 10^9$/l prior to initiating any cycle of treatment (see section 4.2).

In the phase III study, thrombocytopenia typically recovered to baseline by the start of the next 21-day cycle (see Figure 1). The median time to onset for grade 3 and 4 thrombocytopenia 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 CTC 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 4.2 and 4.8).

Haemorrhage

Haemorrhage has been reported in patients during treatment with panobinostat. CTC grade 3 or 4 haemorrhage was reported in 4.2% of patients, including cases of gastrointestinal and pulmonary haemorrhage with fatal outcomes. Therefore, physicians and patients should be aware of the increased risk of thrombocytopenia and the potential for haemorrhage, especially in patients with coagulation disorders or in those who are receiving chronic anti-coagulation therapy.

Infection

Localised 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, or respiratory or multi-organ failure) and have had fatal outcomes (see section 4.8). 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 4.8). Physicians and patients should be aware of the increased risk of infection with panobinostat.

Farydak treatment should not be initiated in patients with active infections. Pre-existing infections should be treated prior to initiation of the therapy. Patients should be monitored for signs and symptoms of infections during treatment with panobinostat; if a diagnosis of infection is made, appropriate anti-infective treatment should be instituted promptly and interruption or discontinuation of Farydak considered.

If a diagnosis of invasive systemic fungal infection is made, panobinostat should be discontinued and appropriate anti-fungal therapy instituted.

Gastrointestinal disorders

Severe nausea, diarrhoea, constipation and vomiting, sometimes requiring the use of anti-emetic and anti-diarrhoeal medicinal products, have been reported in patients treated with Farydak (see section 4.8). 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 4.2).

Prophylactic anti-emetics (e.g. prochlorperazine) may be considered at the discretion of the physician and in accordance with local medical practice. Anti-emetic medicinal products with a known risk of QT prolongation such as dolasetron, granisetron, ondansetron and tropisetron should be used with caution (see section 4.5).

At the first sign of abdominal cramping, loose stools or onset of diarrhoea, it is recommended that the patient be treated with anti-diarrhoeal medicinal product (e.g. loperamide) or any additional treatment in accordance with local treatment guidelines. Replacement intravenous fluids and electrolytes may be used as appropriate. Medicinal products 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 the use of any laxative product.

Electrocardiographic changes

Panobinostat may prolong cardiac ventricular repolarisation (QT interval).

No episodes of QTcF prolongation >500 msec were 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 panobinostat alone in multiple indications and at different dose levels have shown that the incidence of CTC 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 (see section 4.2).

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

Appropriate monitoring of electrolytes (e.g. potassium, magnesium and phosphorus) and ECG should be performed at baseline and periodically during treatment, particularly in patients with severe gastrointestinal adverse drug reaction (see section 4.2).

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

Concomitant administration of medicinal products that are known to cause QTc prolongation should be used with caution (see section 4.5).

In case of concomitant use of agents that may increase panobinostat plasma concentrations, such as strong CYP3A4 inhibitors, dose adjustment is required (see sections 4.5 and 4.2).

Hepatotoxicity

Hepatic dysfunction, primarily mild transient elevations in aminotransferases and total bilirubin, has 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. 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 SmPC and Table 6).

Elderly population

It is recommended to monitor patients over 65 years of age more frequently, especially for thrombocytopenia and gastrointestinal toxicity (see section 4.8 and section 4.2).

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 section 4.2).

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 4.5).

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 4.5 and 4.6 and bortezomib and dexamethasone SmPC). 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 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Farydak metabolism is through both non-CYP and CYP mediated routes. Approximately 40% of panobinostat is metabolised through CYP3A4. Metabolism via CYP2D6 and 2C19 was minor. Therefore, medicinal products that can influence CYP3A4 enzyme activity may alter the pharmacokinetics of panobinostat. Panobinostat is a P-gp substrate.

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-fold, respectively, compared to when panobinostat was given alone.

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, the dose of panobinostat should be reduced (see section 4.2).

Patients should be instructed to avoid star fruit, grapefruit, grapefruit juice, pomegranates and pomegranate juice, as these are known to inhibit cytochrome P450 3A enzymes and may increase the bioavailability of panobinostat.

Agents that are predicted to decrease panobinostat concentrations

The panobinostat fraction metabolised through CYP3A4 is approximately 40%. In clinical studies in multiple myeloma, the exposure of panobinostat was decreased by approximately 20% by the concomitant use of dexamethasone, which is a dose-dependent mild/moderate CYP3A4 inducer. Strong inducers are expected to have greater effects, and 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.

Agents whose plasma concentrations may be increased by panobinostat

Panobinostat increased the C_{max} and the AUC of dextromethorphan (a substrate of CYP2D6) by 1.8- and 1.6-fold, respectively, and it cannot be excluded that the effect may be larger on a more sensitive CYP2D6 substrate. Avoid panobinostat use in patients who are taking CYP2D6 substrates with a narrow therapeutic index (including, but not limited to, pimozide). When Farydak is co-administered with sensitive CYP2D6 substrates (e.g. atomoxetine, dextromethorphan, metoprolol, nebivolol, perphenazine and pimozide), dose titrate individual CYP2D6 substrates based on tolerability and frequently monitor patients 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 medicinal products (including, but not limited to, amiodarone, disopyramide, procainamide, quinidine and sotalol) and other substances that are known to prolong the QT interval (including, but not limited to, chloroquine, halofantrine, clarithromycin, methadone, moxifloxacin, bepridil and pimozide) is not recommended. Anti-emetic medicinal products with a known risk of QT prolongation such as dolasetron, granisetron, ondansetron and tropisetron should be used with caution (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/Contraception in males and females

Based on findings in animals, the likelihood of panobinostat increasing the risk of both foetal death and developmental skeletal abnormalities when administered to pregnant women is predicted to be high. Women of child-bearing potential should have a pregnancy test prior to the initiation of treatment with Farydak and must use a highly effective method of contraception during treatment and for three months after the last dose of Farydak. Women using hormonal contraceptives should additionally use a barrier method of contraception.

Due to its cytostatic/cytotoxic mode of action, panobinostat can influence the quality of sperm formed during treatment. Sexually active men taking Farydak and their female partners should use a highly effective method of contraception during the man's treatment and for six months after his last dose of Farydak.

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 hormonal contraceptives needs to be considered. In addition, it is currently unknown whether panobinostat may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should additionally use a barrier method of contraception.

Pregnancy

There are no clinical studies on the use of Farydak in pregnant patients. Studies in animals have shown reproductive and embryo-foetal toxicity (see section 5.3). Given panobinostat's cytostatic/cytotoxic mode of action, the potential risk to the foetus is high. Farydak should only be used during pregnancy if the expected benefits outweigh the potential risks to the foetus. If it is used during pregnancy or if the patient becomes pregnant while using it, the patient must be informed of the potential risk to the foetus.

Breast-feeding

It is unknown whether panobinostat is excreted in human milk. Given its cytostatic/cytotoxic mode of action, breast-feeding is contraindicated during Farydak treatment (see section 4.3).

Fertility

Based on non-clinical findings, male fertility may be compromised by treatment with Farydak (see section 5.3).

4.7 Effects on ability to drive and use machines

Farydak has a minor influence on the ability to drive and use machines. Dizziness may occur following administration of Farydak (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety data of panobinostat have been assessed from a total of 451 patients with multiple myeloma treated with panobinostat in combination with bortezomib and dexamethasone and from a total of 278 patients treated with panobinostat as a single agent.

The safety data reported below are based on the phase III clinical study (Panorama 1) in 381 patients with multiple myeloma treated with 20 mg panobinostat once a day three times per week, on a 2 weeks on and 1 week off dosing regimen in combination with bortezomib and dexamethasone. The median duration of exposure in the study was 5.0 months. 15.7% of patients were exposed to study treatment for ≥48 weeks.

The most common non-haematological adverse reactions were diarrhoea, fatigue, nausea and vomiting.

Treatment-emergent haematological toxicities included thrombocytopenia, anaemia, neutropenia and lymphopenia.

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.

Cardiac events (most frequently atrial fibrillation, tachycardia, palpitation and sinus tachycardia) were reported in 17.6% of panobinostat + bortezomib + dexamethasone-treated patients versus 9.8% of placebo + bortezomib + dexamethasone-treated patients and syncope events were reported in 6.0% versus 2.4%, respectively.

Discontinuation due to adverse events, regardless of causality, was observed in 36.2% of patients. The most common adverse events (AEs) leading to treatment discontinuation were diarrhoea (4.5%), asthenia and fatigue (2.9% each) and pneumonia (1.3%).

On-treatment deaths not due to the study indication (multiple myeloma) were reported in 6.8% of panobinostat + bortezomib + dexamethasone-treated patients versus 3.2% of placebo + bortezomib + dexamethasone-treated patients.

Tabulated list of adverse drug reactions from clinical studies

Adverse drug reactions from the phase III study (Panorama 1) 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 includes adverse drug reactions that occur due to the addition of panobinostat to the bortezomib and dexamethasone combination. The frequency category reflects the combination of all the medicinal products i.e. panobinostat + bortezomib + dexamethasone. For adverse drug reactions that are related to bortezomib or dexamethasone treatment, please refer to the relevant SmPC.

Table 7 Panobinostat adverse drug reactions observed in multiple myeloma patients in the phase III 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	Haemorrhage intracranial, syncope, tremor, dysgeusia
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
	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

Description of selected adverse drug reactions

Gastrointestinal

Gastrointestinal toxicity, primarily diarrhoea, nausea and vomiting, is among the most frequently reported adverse reactions. However, treatment discontinuation due to these reactions was reported in a relatively small proportion of patients, with diarrhoea at 4.5% and nausea and vomiting at 0.5% each. Patients should be advised to contact their physician if severe gastrointestinal toxicity occurs and dose adjustment or discontinuation may be required (see section 4.4).

Thrombocytopenia

Due to the nature of multiple myeloma and the known haematotoxicity for panobinostat and its combination agent bortezomib, thrombocytopenia, often severe, has been frequently observed. CTC grade 3 or 4 thrombocytopenia occurred in 256 patients, with a median onset time of one month. However, thrombocytopenia is reversible (median time to recovery of 12 days) and can usually be managed by dose adjustment and interruption with or without platelet transfusion (see section 4.4). 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 rarely leads to treatment discontinuation (1.6% of patients). Most patients with thrombocytopenia did not experience haemorrhage. 20.7% of patients experienced haemorrhage, most

frequently epistaxis (4.7%), haematoma (2.6%), and conjunctival haemorrhage (2.1%). CTC grade 3 or 4 haemorrhage was reported in 4.2% of patients, mostly commonly involving gastrointestinal haemorrhage. 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 thrombocytopenia grade 3 and 1 patient had thrombocytopenia grade 1.

Neutropenia
Neutropenia was frequently reported on the basis of laboratory findings determined during the study (all grades: 75%). Most newly occurring severe neutropenia was grade 3 (28%), with considerably fewer cases of grade 4 (6.6%). While many patients developed neutropenia, febrile neutropenia only occurred in a fraction of treated patients (1.0%, both for CTC all grades and for grades 3 and 4). Patients with neutropenia are prone to infection, mostly upper respiratory tract infection or pneumonia. Only 0.3% of the patients were discontinued from the treatment due to neutropenia.

Fatigue and asthenia
Fatigue and asthenia were reported in 41.2% and 22.0% of patients, respectively. CTC 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 CTC grade 4. The treatment was discontinued in 2.9% of patients due to fatigue and asthenia.

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 Farydak treatment. The most frequently reported infections include upper respiratory tract infection, pneumonia and nasopharyngitis. Fatalities involving either pneumonia or sepsis were reported. Treatment discontinuation due to infections was reported in 5% of patients.

QT prolongation and ECG abnormalities
QTc prolongation was observed and was mostly mild in degree: QTcF interval >450 msec and ≤480 msec was reported in 10.8% of patients, with maximum increase from baseline >30 msec and ≤60 msec in 14.5% of patients. QTcF >500 msec was not reported in any patient.

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 population
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, 65-75 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 (16%, 17% and 29%), diarrhoea (21%, 27% and 47%), and fatigue (18%, 28% and 47%).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance
Website: www.hpra.ie.

4.9 Overdose

Limited experience with overdose has been reported during clinical studies. Adverse reactions observed were consistent with the safety profile, with events primarily involving haematological and gastrointestinal 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 whether panobinostat is dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, histone deacetylase (HDAC) inhibitors, ATC code: L01XH03

Mechanism of action

Farydak is a histone deacetylase (HDAC) inhibitor that inhibits the enzymatic activity of HDACs at nanomolar concentrations. HDACs catalyse 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. *In vitro*, panobinostat caused the accumulation of acetylated histones and other proteins, inducing cell cycle arrest and/or apoptosis of some transformed cells. Increased levels of acetylated histones were observed in xenografts from mice that were treated with panobinostat. Panobinostat shows more cytotoxicity towards tumour cells compared to normal cells.

Pharmacodynamic effects

Treatment of tumour cells with panobinostat resulted in a dose-dependent increase in acetylation of histones H3 and H4 both *in vitro* and in xenograft animal pre-clinical models, demonstrating target inhibition. In addition, increased expression of the tumour suppressor gene p21CDKNIA (cyclin dependent kinase inhibitor 1/p21) gene, a key mediator of G1 arrest and differentiation, was triggered with panobinostat exposure.

Clinical efficacy and safety

Clinical efficacy in patients with relapsed and relapsed and refractory multiple myeloma (Study D2308 – Panorama 1)
The efficacy and safety of panobinostat in combination with bortezomib and dexamethasone were evaluated in a randomised, double-blind, placebo-controlled, multicentre phase III 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 taken orally once a day, three times per week, on a 2 weeks on and 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 randomised in a 1:1 ratio to either the panobinostat + bortezomib + dexamethasone (n=387) or the placebo + bortezomib + dexamethasone (n=381) arm, 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% and blacks 2.9%. ECOG performance status was 0-1 in 93% of patients. The median number of prior therapies was 1.0. More than half (57.2%) of the patients had undergone prior stem cell transplantation and 62.8% of the patients were relapsed after previous anti-neoplastic therapies (e.g. melphalan 79.6%, dexamethasone 81.1%, thalidomide 51.2%, cyclophosphamide 45.3%, bortezomib 43.0%, combined bortezomib and dexamethasone 37.8%, 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 + dexamethasone arm and 29.04 months in the placebo + bortezomib + dexamethasone arm.

The primary endpoint was progression free survival (PFS) as per modified European Bone Marrow Transplant Group (mEBMT) 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 + dexamethasone arm compared to the placebo + bortezomib + dexamethasone arm (Hazard ratio: 0.63 (95% CI: 0.52, 0.76)). The median PFS (95% CI) was 12.0 months (10.3, 12.9) and 8.1 months (7.6, 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)).

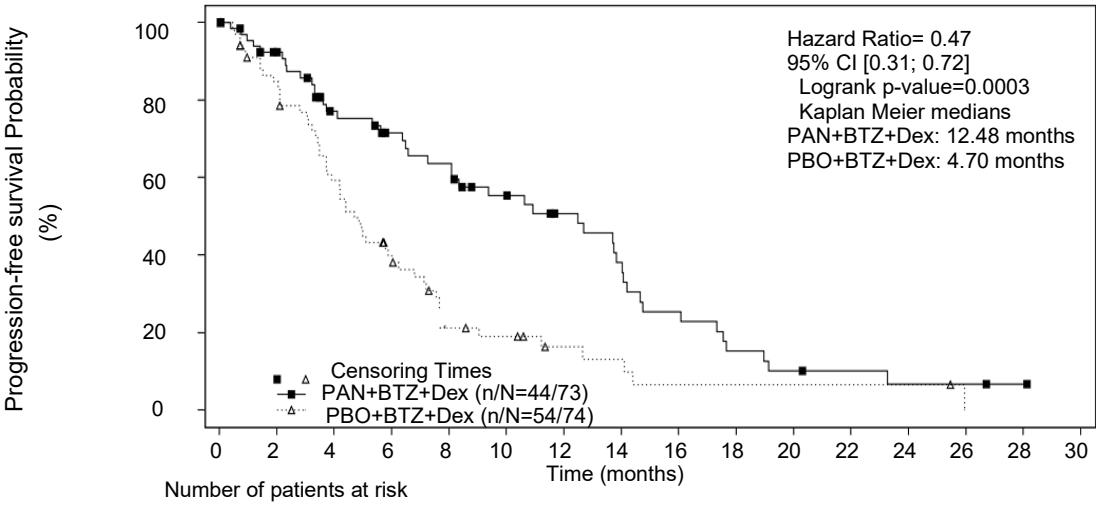
Out of the pre-specified subgroup of patients with prior treatment with bortezomib and an immunomodulatory agent (N=193), 76% of patients had received at least two prior regimens. In this subset of patients (N=147), the median duration of treatment was 4.5 months in the panobinostat + bortezomib + dexamethasone 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 8 and the Kaplan-Meier curves for PFS are provided in Figure 2.

Table 8 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



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

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 9.

Table 9 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	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%)

Clinical efficacy in patients with bortezomib-refractory multiple myeloma (Study DUS71 – Panorama 2)

Study DUS71 was a two-stage, single-arm, open-label multicentre phase II study of oral panobinostat (20 mg) in combination with bortezomib (1.3 mg/m^2) and dexamethasone (20 mg) in 55 patients with relapsed and refractory multiple myeloma, who were bortezomib-refractory and had received at least two prior lines of therapy. Patients had to be exposed to an 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.

The primary endpoint of the study was to assess overall response rate (ORR) after 8 cycles of therapy as per mEBMT criteria.

Patients were heavily pre-treated and had received multiple prior regimens (median: 4; range: 2-11). All 55 patients were previously treated with bortezomib and at least one IMiD (lenalidomide: 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: 0.1-24.1 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.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Farydak in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Panobinostat is rapidly and almost completely 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 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 90%) bound to human plasma proteins. Its fraction in the erythrocyte is 0.60 *in vitro*, independent of the concentration. The volume of distribution of panobinostat at steady state (Vss) is approximately 1,000 litres based on final parameter estimates in the population pharmacokinetic analysis.

Biotransformation

Panobinostat is extensively metabolised, and a large fraction of the dose is metabolised before reaching the systemic circulation. 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 potential minor involvement of CYP2D6 and 2C19.

Panobinostat represented 6 to 9% of the drug-related exposure in plasma. The parent substance 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 faeces. Unchanged panobinostat accounted for <2.5% of the dose in urine and <3.5% of the dose in faeces. 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

Paediatric population
Panobinostat was not evaluated in multiple myeloma patients under 18 years of age.

Elderly population
In the phase III clinical study 162 out of 387 patients were aged 65 years or over. Plasma exposure of panobinostat in patients aged 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 mg and 80 mg.

Patients with hepatic impairment
The effect of hepatic impairment on the pharmacokinetics of panobinostat was evaluated in a phase I study, in 24 patients with solid tumours and with varying degrees of hepatic impairment. Mild and moderate hepatic impairment as per NCI-CTEP classification increased panobinostat plasma exposure by 43% and 105%, respectively. No pharmacokinetic data are available for patients with severe hepatic impairment.

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 function. Mild, moderate and severe renal impairment based on baseline urinary creatinine clearance did not increase the panobinostat plasma exposure in mild, moderate and severe groups.

5.3 Preclinical safety data

Repeated dose toxicity studies

The primary target organs of toxicity following administration of panobinostat in rats and dogs were identified as the erythropoietic, myelopoietic and lymphatic systems. The thyroid changes including hormones in dogs (decrease triodothyronine (T3)) and rats (decrease in triodothyronine (T3), tetraiodothyronine (T4) (males) and thyroid stimulating hormone (TSH)) were observed at exposures corresponding to 0.07-2.2 of the human AUC observed clinically.

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. Additionally, in vivo DNA damage was observed in a COMET study in mouse lymphoma L5178Y cells and a dose-dependent molecular mechanisms study in murine bone marrow cells. The in vitro and in vivo findings are attributed to the pharmacological mode of action.

Reproduction toxicity

An increase in early resorptions was observed in female rats (doses ≥30 mg/kg). Prostatic atrophy accompanied by reduced secretory granules, testicular degeneration, oligospermia and increased epididymal debris were observed in dogs at exposures corresponding to 0.41-0.69 of the human clinical AUC and not fully reversible after a 4 week recovery period.

Based on animal data, the likelihood of panobinostat increasing the risk of foetal death and developmental skeletal abnormalities is predicted to be high. Embryo foetal lethality and increases in skeletal anomalies (extra sternabrae, extra ribs, increases in minor skeletal variations, delayed ossification and variations of the sternabrae) were seen above exposures corresponding to 0.25 of the human clinical AUC.

The effects of panobinostat on labour and post-natal growth and maturation were not evaluated in

animal studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Magnesium stearate
Mannitol
Microcrystalline cellulose
Pregelatinised starch (maize)

Capsule shell

Farydak 10 mg hard capsules
Gelatin
Titanium dioxide (E171)
Brilliant blue FCF (E133)
Iron oxide, yellow (E172)

Farydak 15 mg hard capsules
Gelatin
Titanium dioxide (E171)
Iron oxide, yellow (E172)
Iron oxide, red (E172)

Farydak 20 mg hard capsules
Gelatin
Titanium dioxide (E171)
Iron oxide, red (E172)

Printing ink

Iron oxide, black (E172)
Propylene glycol (E1520)
Shellac glaze

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PCTFE/Alu blister containing 6 capsules.

Packs containing 6, 12 or 24 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

pharmaand GmbH
Taborstrasse 1
1020 Wien
Austria

8. MARKETING AUTHORISATION NUMBER(S)

Farydak 10 mg hard capsules

EU/1/15/1023/001-003

Farydak 15 mg hard capsules

EU/1/15/1023/004-006

Farydak 20 mg hard capsules

EU/1/15/1023/007-009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 August 2015
Date of latest renewal: 28 April 2020

10. DATE OF REVISION OF THE TEXT

28 November 2024

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu