Clin Pharmacokinet (2018) 57:21–29
https://doi.org/10.1007/s40262-017-0565-x

REVIEW ARTICLE

Clinical Pharmacokinetics and Pharmacodynamics of Panobinostat

Mathilde Van Veggel[1] · **Elsbeth Westerman**[1] · **Paul Hamberg**[2]

Published online: 30 June 2017

Abstract Histone deacetylase (HDAC) inhibitors cause an increase in acetylation that leads to an increase in DNA transcription and accumulation of different proteins, reducing cell proliferation and inducing cell death. Panobinostat is a first-in-line HDAC inhibitor approved for treating multiple myeloma in combination with bortezomib and dexamethasone. It is a pan-deacetylase inhibitor and therefore inhibits not only HDAC but also other deacetylases. The main mechanism of action of panobinostat is to inhibit HDAC, which causes cell cycle arrest and apoptosis, leading to it being an antineoplastic drug. Pooled data of multiple-dose studies show that an oral dose of panobinostat 20 mg resulted in a maximum plasma concentration (C_{max}) of 21.6 ng/mL approximately 1 h after administration, while doses between 10 and 30 mg resulted in dose proportional plasma levels. The absolute bioavailability of panobinostat is 21.4%, and it is moderately bound to plasma proteins. Renal impairment does not influence the intrinsic pharmacokinetics of panobinostat, however hepatic impairment causes an increase in the plasma concentrations of this drug. Therefore, starting treatment at lower doses could be considered in patients with mild to moderate hepatic impairment. Different ethnic backgrounds have an influence on the pharmacokinetics of panobinostat; however, due to major interindividual variability, no dose adjustment is recommended. The area under the concentration–time curve of panobinostat changes significantly under cytochrome P450 (CYP) 3A4 inhibitors, CYP3A4 and CYP2D6 inducers, and P-glycoprotein inhibitors. Panobinostat itself is a CYP2D6 inhibitor, which influences the plasma levels of the CYP2D6 substrate dexamethasone. The main side effects of panobinostat are diarrhea, peripheral neuropathy, asthenia and fatigue; hematologic side effects include neutropenia, thrombocytopenia, and lymphocytopenia.

Key Points

Panobinostat is a pan-deacetylase inhibitor that targets, among others, histone deacetylases.

There is high interindividual variability in the population pharmacokinetics of panobinostat.

The pharmacokinetics of panobinostat are influenced by hepatic impairment, cytochrome P450 (CYP; CYP3A4, CYP2D6) and P-glycoprotein interactions and race.

Panobinostat itself is a CYP2D6 inhibitor that influences the plasma levels of concomitantly used dexamethasone.

1 Introduction

Histone deacetylase (HDAC) enzymes play an important role in controlling cell cycle progression, as well as cell survival and differentiation, through the removal of lysine residues, including those of histones. The HDAC enzymes are divided into four subclasses based on their catalytic

✉ Mathilde Van Veggel
m.vanveggel@franciscus.nl

[1] Department of Pharmacy, Franciscus Gasthuis, Rotterdam, The Netherlands

[2] Department of Internal Medicine, Franciscus Gasthuis, Rotterdam, The Netherlands

mechanism, in which 18 types of HDACs are recognized [1, 2]. The removal of lysine residues on histones results, among others, in the epigenetic translation of the DNA as the DNA is more accessible for DNA-binding proteins. However, HDACs have multiple other targets, such as tumor protein p53, heat shock protein 70, and α-tubulin. Through these different targets, HDACs can, on the one hand, be involved in the pathogenesis of cancer and, on the other hand, suppress cancer [3].

HDAC inhibitors cause an increase in acetylation that leads to an increase in DNA transcription and accumulation of different proteins, reducing cell proliferation and inducing cell death (apoptosis). Multiple myeloma is a neoplastic plasma cell disease that evolves from several chromosomal translocations, gene mutations, and epigenetic dysregulations [4]. Therefore, from a theoretical point of view, HDAC inhibitors may be suited to treat multiple myeloma.

Panobinostat is a first-in-line HDAC inhibitor that obtained marketing approval in the US and EU in 2015, and is registered for treating multiple myeloma in combination with bortezomib and dexamethasone in patients who have received at least two prior regimens, including bortezomib and an immunomodulatory agent. It is a pan-deacetylase inhibitor and therefore inhibits not only HDAC but also other deacetylases. The main mechanism of action of panobinostat is to inhibit HDAC, leading to it being an antineoplastic drug. In addition, panobinostat also influences the effects of some non-histone proteins.

In clinical trials, monotherapy of panobinostat did not provide the desired outcomes for efficacy and safety. The combination of panobinostat and bortezomib showed better outcomes in relapsed and refractory myeloma, a synergistic effect that is likely caused by the fact that these agents inhibit different pathways, i.e. the aggresome and proteasome pathways, respectively [5, 6]. As the origin of the disease is multifactorial, optimal treatment is combination therapy with different targets.

Panobinostat is currently tested for other malignant diseases, e.g. relapsed diffuse large B cell lymphoma, non-small cell lung cancer, and breast cancer, in combination with other compounds such as rituximab, erlotinib and letrozole [7–10].

This article reviews the pharmacokinetics of panobinostat, both in general and in specific patient subsets, and the influence of extrinsic factors. In addition, the efficacy and safety of panobinostat will be discussed.

2 Physicochemical Properties

Panobinostat (Farydak®), also known as LBH589 (Fig. 1), is an inhibitor of HDAC subclasses I and IIa/b containing 10 HDAC enzymes, leading to it being a pan-deacetylase inhibitor. It is a cinnamic hydroxamic acid analog, with a molecular weight of 439.51 mol/g for the base form of panobinostat and 349.43 mol/g for the anhydrous lactate form. It is available in hard capsules as anhydrous panobinostat lactate containing 10, 15 and 20 mg panobinostat [11]. Panobinostat has a high solubility, resulting in almost complete absorption [12]. In Caco-2 cells, the in vitro permeability is good [11]. Due to its good solubility and permeability, panobinostat is a Biopharmaceutics Classification System (BCS) class I compound.

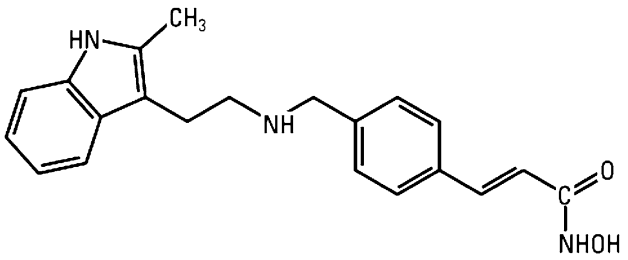

Fig. 1 Structural formula of panobinostat (LBH589, Farydak®): 2-(E)-*N*-hydroxy-3-[4[[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]-methyl]phenyl]-2-propenamide [11]

3 Pharmacokinetics

The pharmacokinetics of panobinostat have been studied in preclinical, phase I and II studies; however, no studies in healthy volunteers have been published, possibly because panobinostat is potentially mutagenic and genotoxic. Preclinical studies are not available in the public domain, although results from phase I and II studies, performed in patients with advanced solid tumors and hematologic malignancies, are available. Specific phase I studies were performed in patients with renal and hepatic impairment. Furthermore, data from studies performed in different ethnic groups and from a study that explored the effect of food on the bioavailability and pharmacokinetics of panobinostat are available. An overview of the main pharmacokinetic parameters following a single dose and multiple doses, as well as population pharmacokinetic data, are presented in Tables 1, 2 and 3 and portrayed in Fig. 2.

3.1 Absorption and Distribution

In a phase I study, the distribution, metabolism, and excretion of panobinostat in eight patients with advanced cancer were studied. The radioactivity in blood, plasma, urine, and feces was determined up to 7 days after dosing. After oral administration of a dose of radioactive ^{14}C-labeled panobinostat, a 3.3% recovery of unchanged panobinostat was found in the feces, suggesting a high systemic absorption of panobinostat [12]. The recovered

Table 1 Pharmacokinetic parameters of a single oral dose of panobinostat [12, 15]

Parameter and unit	Panobinostat dose		
	15 mg ($n = 4$–7) in combination with docetaxel [15]	20 mg ($n = 4$) [12]	20 mg ($n = 4$–8) [15]
C_{max} (ng/mL)	11.8 (94.5), $n = 7$	21.2 (13.4–41.5)	14.3 (51.8), $n = 8$
t_{max} (h)	1.0 (0.5–4.0), $n = 7$	0.8	1.5 (0.5–3.0), $n = 8$
AUC_{24} (ng·h/mL)	65.3 (29.5), $n = 4$	–	81.2 (46.1), $n = 6$
AUC_{∞} (ng·h/mL)	68.7 (26.4), $n = 3$	96 (81–176)	134.3 (51.5), $n = 4$
$t_{½}$ (h)	–	30.7 (27.6–33.2)	–
CL_R/F (L/h)	–	3.2 (2.4–5.5)	–
CL/F (L/h)	–	209 (114–248)	–
V_z/F (L)	–	9464	–

Data are expressed as geometric mean (%CV) or median (range)

C_{max} maximum observed plasma drug concentration, t_{max} time to reach C_{max}, AUC_{24} area under the concentration–time curve from time zero to 24 h, AUC_{∞} area under the concentration–time curve from time zero to infinity, $t_{½}$ elimination half-life, CL_R/F renal clearance, CL/F total body clearance of drug from the plasma, V_z/F apparent volume of distribution, $\%CV$ percentage coefficient of variation

Table 2 Pharmacokinetic parameters of oral panobinostat in multiple-dose studies (pooled data of Fukutomi et al. [14], Rathkopf et al. [15], and San-Miguel et al. [11, 24])

Parameter and unit	Panobinostat dose			
	10 mg ($n = 3$)	15 mg ($n = 7$)	20 mg ($n = 32$)	30 mg ($n = 18$)
C_{max} (ng/mL)	12.7 (191)	12.9 (46)	21.6 (83)	25.3 (97)
t_{max} (h)	1 (0.5–4)	1 (0.4–2)	1 (0.5–8)	2 (0.7–4)
AUC_{24} (ng·h/mL)	77 (75)	139 (71)	174 (92)	174 (92)
AUC_{∞} (ng·h/mL)	163 (65)	158 (46)	200 (53)	288 (67)
$t_{½}$ (h)	17.6 (40)	18.3 (29)	16.9 (33)	16.9 (34)
CL/F (mL/min)	61.5 (65)	94.9 (46)	99.8 (53)	99.9 (70)
V_z/F (L)	1951 (58)	1202 (25)	2337 (53)	2004 (75)

Data are expressed as geometric mean (%CV), except for t_{max}, which is expressed as median (range)

C_{max} maximum observed plasma drug concentration, t_{max} time to reach C_{max}, AUC_{24} area under the concentration–time curve from time zero to 24 h, AUC_{∞} area under the concentration–time curve from time zero to infinity, $t_{½}$ elimination half-life, CL/F total body clearance of drug from the plasma, V_z/F apparent volume of distribution, $\%CV$ percentage coefficient of variation

cumulative excretion of radioactivity in urine and feces was more than 87% in 7 days. Higher radioactivity was found in plasma versus whole blood samples, indicating that panobinostat is more distributed in plasma than in blood cells.

The absolute bioavailability ($F = 21.4\%$) of panobinostat in a population pharmacokinetic study in patients with advanced hematologic and solid tumors was low, probably due to a great first-pass effect [13]. Maximal concentration after oral dosing was reached after 0.5–3 h (see Fig. 2 and Tables 1 and 2) [12, 14–16], and doses between 10 and 30 mg resulted in mean maximum plasma levels of 12.9–25.3 ng/mL.

Based on the data obtained in patients treated with panobinostat 10–30 mg, it was observed that panobinostat has linear pharmacokinetics (Fig. 2) that are dose proportional [13, 16, 17]. Steady-state plasma concentrations of panobinostat were reached approximately after the third dose in a thrice-weekly schedule [12]. In a dose-escalation study, intravenous panobinostat was administered in a daily schedule (days 1–3 and 8–10 of a 21-day cycle; doses between 1.2 and 9.0 mg/m^2) and a thrice-weekly schedule (days 1, 8, and 15 of a 28-day cycle; doses between 10.0 and 20.0 mg/m^2) [18]. Accumulation was only found in the daily schedule. In a dose-escalating study in Japanese patients receiving intravenous panobinostat (10–20 mg/m^2) in a weekly schedule, no significant drug accumulation was found [17]. Panobinostat is moderately bound to plasma protein (approximately 90%) [11, 19]. Table 3 displays the main parameters of a population pharmacokinetic model.

3.2 Metabolism and Elimination

The previously described phase I study of Clive et al. characterized the metabolism and excretion of radiolabeled panobinostat (Fig. 3) [12]. The results showed that

Table 3 Population pharmacokinetic parameters of panobinostat in a typical patient[a] following a 20 mg oral dose (data from intravenous and oral panobinostat dosing) [13]

Parameter and unit	Population mean estimate
$C_{max\ 48}$ (ng/mL)	10.6
AUC_{48} (ng·h/mL)[a]	98.1
AUC_{48} (ng·h/mL)[b] (range)	80–116
$t_{½}$ (h)	37
CL (L/h)	33.1[c]
F (%)	21.4

C_{max48} maximum observed plasma drug concentration from time zero to 48 h, AUC_{48} area under the concentration–time curve from time zero to 48 h, $t_{½}$ elimination half-life, *CL* clearance, *F* absolute bioavailability

[a] Caucasian patient with a body surface area of 1.9 m^2, 61 years of age

[b] Patients with median body surface area and median age across Caucasian, Black, Asian and other race categories

[c] Interpatient variance in clearance was 74%

panobinostat is metabolized through multiple pathways where reduction, hydrolysis, and one- and two-carbon shortening of the hydroxamic acid side chain and glucuronidation are the most prominent, resulting in at least 77 metabolites. The main cytochrome P450 (CYP) pathway is CYP3A4, followed by CYP2D6 and CYP2C19. The primary metabolites found in this study showed no activity of HDAC inhibition, which suggests that the metabolites are not relevant for the efficacy of panobinostat and its side effects. An in vitro study elucidating the structure of CYP3A4 and CYP2D6 metabolites of panobinostat and their biological activity resulted in the same conclusion [20].

3.3 Variability in Exposure

A population pharmacokinetic study of 7834 samples of 581 patients with solid and hematologic tumors showed an interindividual variability in clearance of 74% [13]. Data were collected from 14 intravenous and oral phase I and II studies. Age, race, and body size affected the pharmacokinetics significantly in the covariate analysis but were minor in comparison to the high variability in clearance. Clearance and the central volume compartment were not significantly affected by creatinine clearance at baseline, hepatic function, concomitant medication, and intravenous or oral dosing.

4 Panobinostat Pharmacokinetics in Specific Patient Subsets

Specific intrinsic factors such as age, sex, ethnicity, and renal and hepatic impairment that might influence the pharmacokinetics of panobinostat were studied. No dose adjustments are advised in the different age categories, but extra caution in patients above 65 years of age is advised as the prevalence of side effects may increase [11]. Pediatric patients were not included in any of the trials. Sex had no influence on the population pharmacokinetics; however, age was a significant covariate as the area under the concentration–time curve (AUC) decreased when age increased, but is not clinically relevant compared with the magnitude of interindividual variability [13].

4.1 Pharmacokinetics in Subjects with Renal Impairment

Renal impairment is a specific interest for panobinostat pharmacokinetics given the fact that the target population, i.e. patients with multiple myeloma, is affected by renal impairment, with a prevalence of 50% at presentation [21]. A phase I, open-label, multicenter study elucidated the influence of renal impairment on the pharmacokinetics and safety of panobinostat in patients with normal renal function versus mild, moderate and severe renal impairment [22]. The 37 patients received a single dose of panobinostat 30 mg followed by blood sample collection at 96 h post-dose, thereafter followed by an extension phase in which panobinostat was administered thrice weekly in 28-day

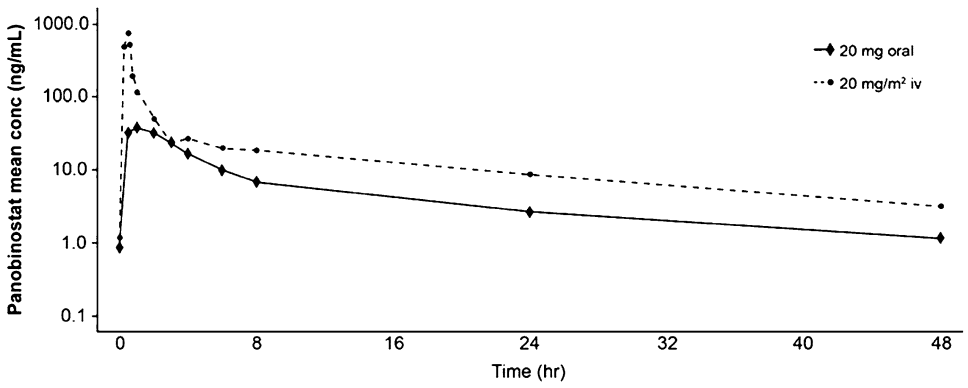

Fig. 2 Plasma concentration–time profiles of panobinostat following a single 20 mg/m^2 intravenous dose and a single 20 mg oral dose. Reproduced from Mu et al. [16]. *conc* concentration, *iv* intravenous

cycles. In case of unacceptable toxicity, dose reductions were indicated. The AUC from time zero to infinity (AUC_{∞}) did not show a trend of increased systemic exposure of panobinostat in the renal impairment groups compared with the patient group with normal renal function (Table 2). The geometric mean ratios of the AUC_{∞} in the group with normal renal function versus mild, moderate, and severe renal impairment were 0.67 [90% confidence interval (CI) 0.39–1.17], 1.05 (90% CI 0.58–1.91), and 0.63 (90% CI 0.33–1.20), respectively. Variations of other pharmacokinetic parameters in mild, moderate, and severe renal impairment are probably caused by small samples sizes and interpatient variability [13]. Serious adverse events (SAEs) were present in 64%, 60%, 40%, and 50% of subjects in the normal, mild, moderate, and severe renal impairment groups. No data were available for end-stage renal disease. Type and tolerance of AEs were similar to the previous studies. In conclusion, no initial dose reduction is advised in patients with renal impairment, and panobinostat is contraindicated in end-stage renal disease because clinical data on these patients are not available [11, 22].

4.2 Pharmacokinetics in Subjects with Hepatic Impairment

In a phase I, single-dose, 1-week pharmacokinetic study of panobinostat 30 mg, pharmacokinetic parameters in patients with solid tumors and hepatic dysfunction (mild, $n = 8$; moderate, $n = 6$; and severe, $n = 1$) versus patients with normal hepatic function ($n = 10$) were assessed (Table 3) [19]. An increase in AUC_{∞} of 43% and 105% in the mild and moderate hepatic function groups, respectively, was observed, likely as a result of the reduced clearance of 30% and 51%. The median time to reach C_{max} (t_{max}) was similar in all groups. No clinically relevant difference in protein binding of panobinostat was observed between groups (normal 83%; mild 83%; moderate 77%; severe 74%). Although there were higher plasma concentrations in the mild and moderate hepatic function groups, no apparent difference in safety outcomes was noted in the safety extension phase. Grade 3 or higher AEs were present in 70%, 63%, and 83% of subjects in the normal, mild, and moderate hepatic function groups, respectively. This study concluded that patients with hepatic impairment can commence treatment with the normal dose of panobinostat, but should be closely monitored and dose adjustments should be considered when adverse events emerge.

Results of the previous study were confirmed by population pharmacokinetic data of panobinostat, which were not significantly influenced by impaired hepatic function [13]. However, the outcome of this study is possibly biased by the design of the included studies, in which patients with hepatic impairment may have been excluded.

In summary, panobinostat exposure may be increased in patients with hepatic dysfunction. Therefore, in contrary to the earlier mentioned studies, the manufacturer advises a lower starting dose of 15 and 10 mg in patients with mild or moderate hepatic impairment, respectively. Dose escalation (15–20 mg and 10–15 mg) can be considered in subsequent cycles based on the degree of toxicity. Due to the fact that no clinical data on patients with severe hepatic impairment are available, panobinostat is contraindicated [11].

4.3 Pharmacokinetics in Subjects of Different Ethnic Background

A population pharmacokinetic study of 14 phase I and II trials showed a significant influence of race on population pharmacokinetics. However, because interindividual variability had the highest contribution to the model, the contribution of race was, in comparison, minor and not significantly relevant [13].

Two phase I, dose-escalating studies performed specifically in Japanese patients with advanced solid tumors showed comparable pharmacokinetics in one study [17], and slightly lower concentrations in the other study compared with previous studies [14].

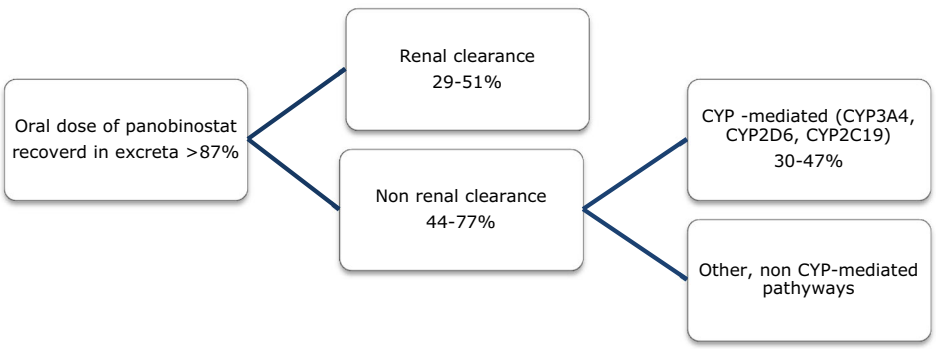

Fig. 3 Schematic of clearance pathways for oral panobinostat 20 mg in eight advanced carcinoma patients over a 7-day period. Based on the data of Clive et al. [12]. *CYP* cytochrome P450

Table 4 Pharmacokinetics of a single oral dose of panobinostat 30 mg in subjects with renal impairment [22]

Parameter and unit	Normal ($n = 11$)	Mild impairment ($n = 10$)	Moderate impairment ($n = 10$)	Severe impairment ($n = 6$)
C_{max} (ng/mL)	31.0 (116.7)	18.2 (68.6)	29.6 (92.5)	14.0 (82.2)
t_{max} (h)	1.02 (0.5–4.0)	1.0 (0.5–4.3)	1.0 (0.5–2)	0.8 (0.5–4)
AUC_{∞} (ng·h/mL)	224.5 (98.6)	144.3 (62.1)	223.1 (76.7)	131.7 (49.5)
$t_{½}$ (h)	29.3 (56.9)	33.1(26.0)	33.0 (21.5)	27.5 (23.8)
CL_R (mL/h)	1.4 (13.0)	1.2 (7.3)	1.3 (5.1)	1.3 (8.6)
CL/*F* (L/h)	27.5 (23.8)	207.9 (62.1)	134.5 (76.7)	227.8 (49.5)
V_z/F (L)	5646 (41.7)	9922 (82.9)	6404 (76.9)	9039 (31.7)

Data are expressed as geometric mean (%CV), except for t_{max}, which is expressed as median (range)

Normal renal function: CrCl > 80 mL/min; mild renal impairment: CrCL ≥ 50 to <80 mL/min; moderate renal impairment: CrCL ≥ 30 to <50 mL/min; severe renal impairment: CrCL < 30 mL/min

C_{max} maximum observed plasma drug concentration, t_{max} time to reach C_{max}, AUC_{∞} area under the concentration–time curve extrapolated from time zero to infinity, $t_{½}$ elimination half-life, CL_R renal clearance, *CL/F* total body clearance of drug from the plasma, V_z/F apparent volume of distribution, *%CV* percentage coefficient of variation, *CrCl* creatinine clearance

5 Effects of Extrinsic Factors on Panobinostat Pharmacokinetics

Extrinsic factors can influence the pharmacokinetics of a drug, for example through drug–drug interactions (DDIs) via CYP interactions, or transporter interactions via P-glycoprotein (P-gp), but absorption interactions with food can also play a role. As earlier described, CYP3A4 is the main route of CYP metabolism of panobinostat, with a less extensive role for CYP2D6 and CYP2C19. Panobinostat is also a substrate for P-gp [11]. An overview of DDI studies with panobinostat is presented in Table 4.

In a DDI study on the effect of ketoconazole, a strong CYP3A4 inhibitor, patients were administered a panobinostat 20 mg dose on days 1 and 8 in combination with a ketoconazole 400 mg dose on days 5–9 [23]. The pharmacokinetic parameters of panobinostat were measured on days 1–3 and 8–10, which resulted in significant differences in C_{max} (18.5 ng/mL without ketoconazole vs. 30.0 ng/mL with ketoconazole; ratio 1.6, 90% CI 1.2–2.2) and AUC_{∞} (133.0 ng·h/mL without ketoconazole vs. 220.7 ng·h/mL with ketoconazole; ratio 1.8, 90% CI 1.5–2.2). No significant differences were measured for t_{max} and elimination half-life ($t_{½}$). Strong CYP3A4 inhibitors increase the AUC ratio by 1.8, resulting in a dose reduction to a dose of 10 mg [11]. Dose titration can be considered based on tolerance.

In a phase Ib study, the effect of dexamethasone on the pharmacokinetics of panobinostat (20 mg dose) and bortezomib (1.3 mg/m^2 dose) was studied as a secondary endpoint [24]. The addition of dexamethasone, added during the second cycle of the expansion phase, resulted in a decrease in panobinostat levels of approximately 20% [AUC from time zero to 24 h (AUC_{24}) 61.8 ng·h/mL (60.9 percentage coefficient of variation; CV%) without dexamethasone vs. 47.5 ng·h/mL (76.8 CV%) with dexamethasone; C_{max} 9.5 ng/mL (60.4 CV%) without dexamethasone vs. 8.1 ng/mL (90.3 CV%) with dexamethasone]. The authors relate this to the CYP3A4-inducing effects of dexamethasone. As dexamethasone is also a CYP2D6 inducer, CYP2D6 induction may furthermore contribute to this effect [25].

The CYP2D6-inducing potential of panobinostat was explored in a DDI study between panobinostat and the CYP2D6 substrate dextromethorphan [26]. The plasma concentration of dextromethorphan (60 mg) with and without a panobinostat 20 mg dose was determined. When panobinostat was coadministered with dextromethorphan, the AUC_{∞} of dextromethorphan increased by 64% (90% CI 1.2–2.3) and the C_{max} increased by 83% (90% CI 1.4–2.3). The use of CYP2D6 substrates with a narrow therapeutic range should be avoided or the CYP2D6 substrate dose should be titrated.

In an in vitro study in Caco-2 cells, panobinostat was shown to be a P-gp substrate [11]. No in vivo studies were performed to evaluate the effect of P-gp inhibitors on panobinostat plasma concentrations, therefore a dose reduction to 10 mg is advised when P-gp inhibitors are concomitantly used.

Food did not have a major effect on the pharmacokinetics and safety of panobinostat [27]. In a randomized, crossover food-effect study, patients with advanced cancer received panobinostat 20 mg in three different prandial states: fasting, normal breakfast, and high-fat breakfast. The AUC_{∞} ratio was 0.84 (90% CI 0.74–0.96) in the high-fat vs. fasting groups, and 0.86 (90% CI 0.75–1.00) in the normal vs. fasting groups. An increase in t_{max} and a decrease in C_{max} was observed in the normal and high-fat breakfast groups, however the $t_{½}$ remained the same in all groups. The drug was tolerated in all groups. Therefore,

panobinostat can be taken irrespective of the intake of food.

6 Clinical Pharmacodynamics of Panobinostat

6.1 Efficacy

The registration of panobinostat for multiple myeloma is mainly based on the pivotal PANORAMA-1 study [28]. This phase III study in 768 patients with relapsed multiple myeloma studied the efficacy and safety of panobinostat in combination with bortezomib and dexamethasone. Treatment consisted of a 3-week cycle of oral panobinostat 20 mg thrice weekly for 2 weeks, or placebo, bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11, and oral dexamethasone 20 mg administered after bortezomib. The study showed a median progression-free survival (PFS) of 11.99 months (95% CI 10.33–12.94) in the panobinostat, dexamethasone and bortezomib group versus 8.08 months (95% CI 7.56–9.23) in the placebo, dexamethasone and bortezomib group, corresponding to a hazard ratio (HR) of 0.63 (95% CI 0.52–0.76). The subgroup analysis for PFS did not show a significant difference between the two groups of patients <65 and >65 years of age in this study, in which 42% of patients were aged 65 years or older. As a secondary endpoint, overall survival (OS) was studied, showing a modest, but not statistically significant, effect. The median OS was 40.3 months (95% CI 35.0–44.8) in the panobinostat group versus 35.8 months (95% CI 29.0–40.6) in the placebo group, corresponding to an HR of 0.94 (95% CI 0.78–1.14) [29].

6.2 Safety

A phase I, dose-escalation study of intravenous panobinostat in patients with lymphoma or solid tumor showed that the side effects of panobinostat increased with increasing dose, which caused a dose-dependent discontinuation of panobinostat due to AEs. Thrombocytopenia was the most frequent SAE in the different dosing groups.

The maximum tolerated dose (MTD) of intravenous panobinostat as a single agent was determined at 20 mg/m^2 weekly in two phase I studies [17, 18]. In a daily schedule, the MTD of intravenous panobinostat was 7.2 mg/m^2 [18]. In a phase Ia/II study, panobinostat 60 mg biweekly was determined as the MTD in patients with multiple myeloma or lymphoma when administered as monotherapy; however, a weekly dose of panobinostat 60 mg exceeded the MTD in this patient group. Therefore, although not studied, a weekly dose of 40 mg was recommended. In patients with myeloid disorders or leukemia, the MTD was determined at panobinostat 60 mg weekly, as well as biweekly [30].

The MTD of oral panobinostat in a phase Ib study in combination with bortezomib and dexamethasone was 20 mg in a thrice-weekly schedule [24]. A 1-week treatment holiday of panobinostat was introduced in the expansion phase. No decrease in efficacy compared with a weekly cycle was observed, while the tolerability for the drug in this study increased; however AEs led to discontinuation in 37% of patients.

Safety was one of the secondary endpoints in the PANORAMA-1 study [16, 28]. In the panobinostat group, 96% of patients developed grade 3–4 AEs versus 82% in the placebo group. The main AEs in both groups were diarrhea, peripheral neuropathy, asthenia, and fatigue, whereas hematologic AEs were neutropenia, thrombocytopenia, and lymphocytopenia. All AEs were more frequent in the panobinostat group. Also in the panobinostat group, 34% of patients discontinued treatment, 2% of whom were due to thrombocytopenia, versus 17% of patients in the placebo group, none of whom were due to thrombocytopenia. Platelets recovered to baseline in the rest week.

In the phase II PANORAMA-2 study, thrombocytopenia occurred in 64% of patients, leading to dose reduction or dose interruption in 42% of patients ($n = 23$), with 44% ($n = 24$) receiving one or more platelet transfusions. No patients dropped out as a result of thrombocytopenia [31].

In the performed studies, there was special interest in the possible cardiac toxicity of panobinostat and its metabolites. In a phase I study, several cardiac AEs were observed in the different treatment arms, i.e. T-wave inversions, Fridericia-corrected QT interval (QTcF) >500 ms, QTcF change >60 ms from baseline, sinus tachycardia (ST) segment depression, hypotension, and transient study drug infusion-associated mild hypotension, among others [18]. Sinus bradycardia, torsade de pointes, a left bundle branch block, and grade-prolonged QTc were dose-limiting cardiac AEs and led to the discontinuation of panobinostat. In this study, these AEs occurred at intravenous doses of 9.0–25.0 mg/m^2. The phase II PANORAMA-2 study, where oral doses of panobinostat 20 mg thrice weekly were administered, showed no significant deviations on the heart [31], while the phase III PANORAMA-1 study showed T-wave changes (40% panobinostat vs. 18% placebo), QTcF change >60 ms from baseline ($n = 3$ panobinostat vs. $n = 4$ placebo), and ST-T segment changes (22% panobinostat vs. 3% placebo) [28]. Hence, an electrocardiogram (ECG) should be performed and electrolytes obtained before the start of therapy, and should be monitored periodically during treatment [11] (Tables 5, 6).

Table 5 Pharmacokinetics of a single oral dose of panobinostat 30 mg in subjects with hepatic impairment [19]

Parameter and unit	Normal ($n = 10$)	Mild impairment ($n = 7$)	Moderate impairment ($n = 6$)	Severe impairment ($n = 1$)
C_{max} (ng/mL)	18.5 (81.2)	29.1 (57.3)	33.9 (50.9)	31.2 (NE)
t_{max} (h)	2.0 (0.5–7.0)	2.0 (0.5–4.0)	2.0 (1.0–4.0)	2.0 (2.0–2.0)
AUC_{∞} (ng·h/mL)	150.3 (72.3)	214.8 (56.3)	308.0 (44.2)	272.3 (NE)
$t_{½}$ (h)	28.8 (27.3)	26.3 (27.6)	34.6 (31.5)	19.9 (NE)
V_z/F (mL)	8,295,077 (54.7)	5,826,678 (48.1)	4,863,991 (35.1)	3,156,940 (NE)
CL/F (mL/h)	199,647 (72.3)	139,658 (56.3)	97,399 (44.2)	110,187 (NE)

Data are expressed as geometric mean (%CV), except for t_{max}, which is expressed as median (range)

Degree of hepatic dysfunction is presented and conforms to The National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria [19]

C_{max} maximum observed plasma drug concentration, t_{max} time to reach C_{max}, AUC_{∞} area under the concentration–time curve extrapolated from time zero to infinity, $t_{½}$ elimination half-life, *CL/F* total body clearance of drug from the plasma, V_z/F apparent volume of distribution, *NE* not evaluable

Table 6 CYP isoenzymes and transporters modulated [11, 23, 24, 26]

Type of study	Perpetrator drug	Metabolic CYP enzymes inhibited	Metabolic CYP enzymes induced	Transporters inhibited	Transporters induced
DDI study	Ketoconazole	CYP3A4		–	–
Phase IB study	Dexamethasone	–	CYP3A4, CYP2D6	–	–
DDI study	Panobinostat	CYP2D6	–	–	–
Preclinical study		–	–	P-gp	–

CYP cytochrome P450, *DDI* drug–drug interaction, *P-gp* P-glycoprotein

7 Summary and Conclusions

Panobinostat is a first-in-line HDAC inhibitor that obtained marketing approval for the treatment of multiple myeloma in combination with bortezomib and dexamethasone. It is almost fully absorbed in the gastrointestinal tract, with a t_{max} of 1 h and a corresponding C_{max} of 21.6 ng/mL after multiple doses of panobinostat 20 mg, an AUC_{24} of 174 ng·h/mL, and a $t_{½}$ of 16.9 h. It has an absolute bioavailability of 21.4%, likely due to a great first-pass effect. Plasma concentrations increase linearly in doses between 10 and 30 mg. Panobinostat is moderately bound to plasma protein and is extensively metabolized through the liver (44–77%), leading to at least 77 metabolites, which do not show activity of HDAC inhibition. Panobinostat and its metabolites are mainly eliminated via urine and feces. A priori dose reduction for patients with renal impairment is not necessary, however a lower starting dose in patients with hepatic impairment could be considered.

Panobinostat showed an increase in PFS in patients with relapsed multiple myeloma when added to treatment with bortezomib and dexamethasone [11.99 months (95% CI 10.33–12.94) vs. 8.08 months (95% CI 7.56–9.23)]. This increase in PFS corresponded to an HR of 0.63 (95% CI 0.52–0.76).

In combination with bortezomib and dexamethasone, the incidence of grade 3 and 4 AEs is high (96%). The side effects of panobinostat are dose-dependent, and the most frequently observed general adverse events are diarrhea, peripheral neuropathy, asthenia, and fatigue. Furthermore, frequently seen hematologic side effects are thrombocytopenia, neutropenia, and lymphocytopenia, whereas thrombocytopenia is generally dose-limiting. In the dose schemes with a rest week, platelets recovered before the start of a new cycle.

Compliance with Ethical Standards

Funding No sources of funding were used to assist in the preparation of this review.

Conflict of interest Mathilde van Veggel owns stock in Novartis. Elsbeth Westerman and Paul Hamberg have no conflicts of interest that are relevant to the content of this review.

References

1. Dokmanovic M, Clarke C, Marks PA. Histone deacetylase inhibitors: overview and perspectives. Mol Cancer Res. 2007;5(10):981–9.
2. de Ruijter AJ, van Gennip AH, Caron HN, Kemp S, van Kuilenburg AB. Histone deacetylases (HDACs): characterization of the classical HDAC family. Biochem J. 2003;370(Pt 3):737–49.
3. Mahlknecht U, Hoelzer D. Histone acetylation modifiers in the pathogenesis of malignant disease. Mol Med. 2000;6(8):623–44.
4. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med. 2011;364(11):1046–60.
5. Ocio EM, Vilanova D, Atadja P, Maiso P, Crusoe E, Fernandez-Lazaro D, et al. In vitro and in vivo rationale for the triple combination of panobinostat (LBH589) and dexamethasone with either bortezomib or lenalidomide in multiple myeloma. Haematologica. 2010;95(5):794–803.
6. Hideshima T, Bradner JE, Wong J, Chauhan D, Richardson P, Schreiber SL, et al. Small-molecule inhibition of proteasome and aggresome function induces synergistic antitumor activity in multiple myeloma. Proc Natl Acad Sci USA. 2005;102(24):8567–72.
7. Gray JE, Haura E, Chiappori A, Tanvetyanon T, Williams CC, Pinder-Schenck M, et al. A phase I, pharmacokinetic, and pharmacodynamic study of panobinostat, an HDAC inhibitor, combined with erlotinib in patients with advanced aerodigestive tract tumors. Clin Cancer Res. 2014;20(6):1644–55.
8. Takhar HS, Singhal N, Gowda R, Penniment M, Takhar P, Brown MP. Phase I study evaluating the safety and efficacy of oral panobinostat in combination with radiotherapy or chemoradiotherapy in patients with inoperable stage III non-small-cell lung cancer. Anticancer Drugs. 2015;26(10):1069–77.
9. Tan WW, Allred JB, Moreno-Aspitia A, Northfelt DW, Ingle JN, Goetz MP, et al. Phase I study of panobinostat (LBH589) and letrozole in postmenopausal metastatic breast cancer patients. Clin Breast Cancer. 2016;16(2):82–6.
10. Assouline SE, Nielsen TH, Yu S, Alcaide M, Chong L, MacDonald D, et al. Phase 2 study of panobinostat with or without rituximab in relapsed diffuse large B-cell lymphoma. Blood. 2016;128(2):185–94.
11. Committee for Medicinal Products for Human Use (CHMP). Farydak. Assessment report. EMEA/H/C/003725/0000. European Medicines Agency; 2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003725/WC500193300.pdf. Accessed 28 Oct 2016.
12. Clive S, Woo MM, Nydam T, Kelly L, Squier M, Kagan M. Characterizing the disposition, metabolism, and excretion of an orally active pan-deacetylase inhibitor, panobinostat, via trace radiolabeled 14C material in advanced cancer patients. Cancer Chemother Pharmacol. 2012;70(4):513–22.
13. Savelieva M, Woo MM, Schran H, Mu S, Nedelman J, Capdeville R. Population pharmacokinetics of intravenous and oral panobinostat in patients with hematologic and solid tumors. Eur J Clin Pharmacol. 2015;71(6):663–72.
14. Fukutomi A, Hatake K, Matsui K, Sakajiri S, Hirashima T, Tanii H, et al. A phase I study of oral panobinostat (LBH589) in Japanese patients with advanced solid tumors. Invest New Drug. 2012;30(3):1096–106.
15. Rathkopf D, Wong BY, Ross RW, Anand A, Tanaka E, Woo MM, et al. A phase I study of oral panobinostat alone and in combination with docetaxel in patients with castration-resistant prostate cancer. Cancer Chemother Pharmacol. 2010;66(1):181–9.
16. Mu S, Kuroda Y, Shibayama H, Hino M, Tajima T, Corrado C, et al. Panobinostat PK/PD profile in combination with bortezomib and dexamethasone in patients with relapsed and relapsed/refractory multiple myeloma. Eur J Clin Pharmacol. 2016;72(2):153–61.
17. Morita S, Oizumi S, Minami H, Kitagawa K, Komatsu Y, Fujiwara Y, et al. Phase I dose-escalating study of panobinostat (LBH589) administered intravenously to Japanese patients with advanced solid tumors. Invest New Drug. 2012;30(5):1950–7.
18. Sharma S, Beck J, Mita M, Paul S, Woo MM, Squier M, et al. A phase I dose-escalation study of intravenous panobinostat in patients with lymphoma and solid tumors. Invest New Drug. 2013;31(4):974–85.
19. Slingerland M, Hess D, Clive S, Sharma S, Sandstrom P, Loman N, et al. A phase I, open-label, multicenter study to evaluate the pharmacokinetics and safety of oral panobinostat in patients with advanced solid tumors and various degrees of hepatic function. Cancer Chemother Pharmacol. 2014;74(5):1089–98.
20. Fredenhagen A, Kittelmann M, Oberer L, Kuhn A, Kuhnol J, Delemonte T, et al. Biocatalytic synthesis and structure elucidation of cyclized metabolites of the deacetylase inhibitor panobinostat (LBH589). Drug Metab Dispos. 2012;40(5):1041–50.
21. Yadav P, Cook M, Cockwell P. Current trends of renal impairment in multiple myeloma. Kidney Dis (Basel). 2016;1(4):241–57.
22. Sharma S, Witteveen PO, Lolkema MP, Hess D, Gelderblom H, Hussain SA, et al. A phase I, open-label, multicenter study to evaluate the pharmacokinetics and safety of oral panobinostat in patients with advanced solid tumors and varying degrees of renal function. Cancer Chemother Pharmacol. 2015;75(1):87–95.
23. Hamberg P, Woo MM, Chen LC, Verweij J, Porro MG, Zhao L, et al. Effect of ketoconazole-mediated CYP3A4 inhibition on clinical pharmacokinetics of panobinostat (LBH589), an orally active histone deacetylase inhibitor. Cancer Chemother Pharmacol. 2011;68(3):805–13.
24. San-Miguel JF, Richardson PG, Gunther A, Sezer O, Siegel D, Blade J, et al. Phase Ib study of panobinostat and bortezomib in relapsed or relapsed and refractory multiple myeloma. J Clin Oncol. 2013;31(29):3696–703.
25. Indiana University, School of Medicine. Flockhart Table™ [updated 2016]. Available at: http://medicine.iupui.edu/clinpharm/ddis/main-table. Accessed 27 June 2017.
26. Feld R, Woo MM, Leighl N, Shepherd FA, Beck JT, Zhao L, et al. A clinical investigation of inhibitory effect of panobinostat on CYP2D6 substrate in patients with advanced cancer. Cancer Chemother Pharmacol. 2013;72(4):747–55.
27. Shapiro GI, Frank R, Dandamudi UB, Hengelage T, Zhao L, Gazi L, et al. The effect of food on the bioavailability of panobinostat, an orally active pan-histone deacetylase inhibitor, in patients with advanced cancer. Cancer Chemother Pharmacol. 2012;69(2):555–62.
28. San-Miguel JF, Hungria VT, Yoon SS, Beksac M, Dimopoulos MA, Elghandour A, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol. 2014;15(11):1195–206.
29. San-Miguel JF, Hungria VT, Yoon SS, Beksac M, Dimopoulos MA, Elghandour A, et al. Overall survival of patients with relapsed multiple myeloma treated with panobinostat or placebo plus bortezomib and dexamethasone (the PANORAMA 1 trial): a randomised, placebo-controlled, phase 3 trial. Lancet Haematol. 2016;3(11):e506–15.
30. DeAngelo DJ, Spencer A, Bhalla KN, Prince HM, Fischer T, Kindler T, et al. Phase Ia/II, two-arm, open-label, dose-escalation study of oral panobinostat administered via two dosing schedules in patients with advanced hematologic malignancies. Leukemia. 2013;27(8):1628–36.
31. Richardson PG, Schlossman RL, Alsina M, Weber DM, Coutre SE, Gasparetto C, et al. PANORAMA 2: panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma. Blood. 2013;122(14):2331–7.