Vilaprisan is a highly potent selective progesterone receptor modulator in development for the treatment of symptomatic uterine fibroids and endometriosis. Its pharmacokinetics are characterized by rapid absorption, almost complete bioavailability, and dose-proportional exposure. The intrinsic factors of age, bodyweight, and race have no clinically relevant effect on the pharmacokinetics and pharmacodynamics of vilaprisan and do not warrant a dose adjustment. Similarly, vilaprisan can be used in patients with mild or moderate renal or hepatic impairment without dose adjustment, but its use is not recommended in patients with severe organ impairment. Vilaprisan has no perpetrator potential on cytochrome P450 (CYP) enzymes or transporters and therefore restrictions in the concomitant use of their substrates are not required. Nonetheless, because it is a sensitive CYP3A4 substrate itself, concomitant use of vilaprisan with strong CYP3A inhibitors or inducers is not recommended. However, there is no risk for QTc prolongation when vilaprisan and a strong CYP3A inhibitor are administered concomitantly, as indicated by a vilaprisan concentration–QTc response analysis across all studies with triplicate electrocardiogram measurements. Furthermore, due to its mode of action, vilaprisan is also not recommended to be used together with progesterin-containing oral contraceptives. Vilaprisan shows a steep exposure–response relationship for inducing amenorrhea in patients with uterine fibroids experiencing heavy menstrual bleeding. Based on simulations, a dose of 2 mg/day is expected to induce a maximum bleeding reduction and was thus selected for phase III.

Key Points

Vilaprisan is a highly potent selective progesterone receptor modulator in development for the treatment of symptomatic uterine fibroids and endometriosis.

Its clinical pharmacology was exhaustively investigated in a large number of phase I and II studies, the results of which are summarized this paper.

Thus, the present paper offers a synopsis of the current state of knowledge of vilaprisan’s clinical pharmacology profile and provides guidance to clinicians.

1 Introduction

Vilaprisan is a highly potent selective progesterone receptor modulator (SPRM) developed for the treatment of symptomatic uterine fibroids (UFs) and endometriosis. It has potent antagonistic activity at the progesterone receptor (PR) but no agonistic activity [1].

UFs are the most common benign smooth muscle tumors of the myometrium [2] and can be found in up to 40% of women aged between 35 and 40 years [3]. Symptoms include heavy menstrual bleeding, which can lead to anemia and fatigue, painful periods, abdominal protuberance, painful intercourse, pelvic pressure, and bladder or bowel dysfunction. Furthermore, UFs can have adverse effects on fertility and pregnancy [4].

UF growth is estrogen- and, most importantly, progesterone-dependent. Therefore, current pharmacological treatment options aim at suppressing or modulating these ovarian
sex hormones, e.g., by means of gonadotropin-releasing hormone (GnRH) agonists or antagonists. Other treatment options are aromatase inhibitors, oral contraceptives, and levonorgestrel-releasing intrauterine systems [5].

In a recent review of the current data on the efficacy and tolerability of vilaprisan, Ciebiera et al. [6] concluded that vilaprisan was effective in ameliorating UF-related clinical symptoms in phase I and II studies and that its tolerability tends to be more favorable than that of GnRH-agonists.

In this paper, we give an overview on the clinical pharmacology data obtained up to phase II of the clinical development of vilaprisan for the indication treatment of symptomatic UFs (electronic supplementary material [ESM] 1). Most studies in this program have already been published individually or have been accepted for publication; studies not yet published are summarized in ESM 2.

Focusing on the possible impact of intrinsic and extrinsic factors on the pharmacokinetics (PK) and pharmacodynamics (PD) of the drug and the analysis of the relationship between PK and PD in patients with UFs, this overview is intended to provide a practical guidance to clinicians.

2 Physicochemical Properties and Preclinical Pharmacology

2.1 Physicochemical Properties

Vilaprisan \{(11β,17β)-17-hydroxy-11-[4(methylsulfonyl)phenyl]-17-(pentafluoroethyl)estra 4,9-dien-3-one\} (Fig. 1) is a highly lipophilic compound with a molecular weight of 544.6 g/mol. It is poorly soluble in aqueous solution under acidic and neutral conditions (< 0.1 mg/100 mL) and shows a high permeability in the Caco-2 cell assay. Therefore, it is a class II drug according to the Biopharmaceutics Classification System (low solubility, high permeability) and also according to the Biopharmaceutics Drug Disposition Classification System (low solubility, extensive metabolism) [7], as it is almost completely eliminated via metabolism.

2.2 Mode of Action and Preclinical Pharmacology

In vitro, vilaprisan exhibits highly selective binding affinity to the human PR [8]. It exhibits no agonistic activity in the PR isoform-specific transactivation assays, but inhibits both PR B and PR A, with half maximal inhibitory concentration (IC$_{50}$) values of 0.09 nM and 0.095 nM, respectively.

Vilaprisan shows no glucocorticoid, mineralocorticoid, anti-mineralocorticoid, estrogenic, or anti-estrogenic activity. The anti-glucocorticoid activity in vitro is significantly lower compared with the standard antagonist mifepristone (Table 1). Following multiple-dose administrations of vilaprisan 0.1, 0.5, 1.0, 2.0 and 5.0 mg to premenopausal women over 84 days, no change from baseline in cortisol values was observed up to the maximum tested dose of 5 mg, suggesting no counter-regulation of the hypothalamic-pituitary-adrenal axis as a consequence of clinically relevant glucocorticoid receptor antagonism (data on file, Bayer AG). Adrenocorticotropic hormone concentrations were not measured in clinical pharmacology studies with vilaprisan.

The high antagonistic activity at the PR could also be demonstrated in several in vivo models, including an inhibitory activity on the progesterone-induced differentiation of the endometrium in the rabbit model as well as complete termination of pregnancy in the rat at a dose of 0.5 mg/kg/day subcutaneously and orally, showing approximately a tenfold higher potency than mifepristone.

Exploratory analysis of the messenger RNA (mRNA) expression profile in endometrial tissue of healthy women treated with different doses of vilaprisan showed that the majority of genes were highly downregulated. These genes were involved in processes directly related to cell-cycle regulation/progression or control of cell growth (partly overexpressed in endometrial carcinoma and other malignant tumors), including genes such AURKA, CCNB1, DLGAP5, EIF4EBP1, FOXM1, HOXA10, MELK, MKI67, MYC. Almost all PD effects were reversible or reduced after the first bleeding after treatment [9].

![Vilaprisan structural formula appearing as a steroid substructure](image-url)
3 Pharmacokinetic (PK) Properties

3.1 General PK in Humans

All data presented in this section were collected in populations of healthy postmenopausal women, mainly Caucasians, unless otherwise stated. Vilaprisan was generally administered in the form of 2 or 5 mg immediate-release tablets, and the validated liquid chromatography-tandem mass spectrometry method described by Liu et al. [10] was used to determine vilaprisan in plasma. A condensed overview of the absorption, distribution, and elimination characteristics of vilaprisan in humans is given in Fig. 2.

Vilaprisan plasma concentration–time curves obtained after single and multiple administration of different doses of vilaprisan are shown in Fig. 3.

3.1.1 Absorption

After oral administration in the form of immediate-release tablets, vilaprisan is rapidly and almost completely absorbed, with times to maximum observed plasma concentrations ($C_{\text{max}}$) between 1 and 2 h after single-dose administration [11, 12]. Food intake, as shown below, has a negligible impact on the PK of vilaprisan [13].
The systemic exposure of vilaprisan, expressed as area under the plasma concentration–time curve from time zero to infinity (AUC) after single-dose administration, or to 24 h after multiple-dose administration (AUC_{24md}), increases approximately dose-proportionally in the dose range 1–30 mg. It accumulates after multiple dosing, with a factor in the range of 1.85–3.19 as expected based on the observed half-lives (31–38 h), indicating linear PK of vilaprisan in the expected therapeutic dose range up to the maximum tested dose, which exceeds the therapeutic dose by a factor of 15 [12]. Vilaprisan exposure shows low interindividual variability in healthy individuals (geometric mean coefficient of variation [CV]) after multiple dosing of approximately 20–40% for AUC_{24md} and 17–30% for C_{max,md}.

The absolute oral bioavailability was determined to be approximately 60% [11], primarily reflecting the contribution of presystemic metabolic first-pass during oral absorption. The overall systemic bioavailability of the immediate-release tablet was similar to that of an oral solution (estimated AUC ratio, 89.0%), whereas the rate of absorption was clearly decreased (estimated C_{max} ratio, 62.1%) [data on file, Study 14720, Bayer AG; ESM 3].

### 3.1.2 Distribution

Vilaprisan is mainly distributed into plasma, with a blood:plasma partition coefficient of between 0.71 and 0.76 [11]. It is moderately and fully reversibly bound to human plasma proteins, showing a fraction unbound of 5.29% in vitro, which is not concentration-dependent; the main binding components are serum albumin and α-1 acid glycoprotein (data on file, Bayer AG). Vilaprisan shows a relevant affinity to tissues, as indicated by a geometric mean steady-state distribution volume (V_{ss}) of approximately 360 L [11].

Based on studies in rats, it can be assumed that there is no relevant penetration of vilaprisan across the blood–brain barrier and the placental barrier, and that excretion in milk is low. Following administration of radiolabeled vilaprisan to lactating rats, an estimated 1% of the dose was excreted in milk (data on file, Bayer AG).

### 3.1.3 Metabolism and Elimination

Vilaprisan is a low to moderate clearance drug with an average systemic clearance of approximately 7 L/h in healthy subjects [11]. The mean terminal half-lives determined in different PK studies after single or multiple oral administration of vilaprisan doses between 1 and 30 mg were in the range of approximately 31–38 h [11, 12]. Vilaprisan is almost exclusively eliminated via metabolic processes (see Fig. 4 for the proposed main metabolic pathways of vilaprisan in humans. Following oral administration of radiolabeled vilaprisan to healthy subjects, vilaprisan was the dominant compound in plasma. No major plasma metabolites exceeding 10% of drug-related AUC were detected [11]. The main biotransformation pathways are oxidations at the steroid skeleton, as well as reductions in the 3-keto moiety and combinations of both. The formation of oxidation products is mainly catalyzed by CYP3A4; the reduction at the 3-keto moiety is catalyzed by aldoketoreductases [11].
The pivotal role of CYP3A4 responsible for the oxidation reactions in the elimination of vilaprisan was confirmed in drug–drug interaction (DDI) studies with the strong CYP3A4 inhibitor itraconazole and the strong CYP3A4 inducer rifampicin (see Sect. 3.2.3.2 and Sect. 5.1). Vilaprisan is excreted predominantly as metabolites via the biliary/fecal route (74%; 13% via the renal route [11]). Excretion of unchanged vilaprisan accounts for < 2%. Overall, 37% of the dose is eliminated by oxidative biotransformation and 24% by a combined oxidation/reduction reaction. Approximately 24% of the dose could not be allocated to specific metabolites and 13% of the radioactivity was not recovered.

### 3.1.4 Digression: Hepatic Safety of Vilaprisan

In all subjects treated with vilaprisan in phase I and II studies, no relevant changes in liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], γ-glutamyltransferase [γ-GT], bilirubin) were observed, and serum liver enzyme level assessment indicated no safety concerns. A very low dose of vilaprisan 2–4 mg was found to be efficacious. Despite high lipophilicity, none of the known risk factors for drug-induced liver injury [14] were found to be applicable for vilaprisan (e.g., no inhibition of bile-acid transporters or bilirubin metabolism, no hint on structural alerts leading to formation of reactive intermediates or covalent binding, no hint on mechanism-based inhibition of CYP enzymes, no mitochondrial or other cell toxicity). In contrast, liver safety signals have been observed with other SPRMs during clinical development, including telapristone and ulipristal acetate, which resulted in either termination of clinical development (telapristone) or severe restrictions in clinical use (ulipristal acetate). Furthermore, mifepristone, currently in single-dose clinical use, showed hints of liver effects after longer-term treatment in a clinical trial [15], as well as in preclinical studies [16]. All these SPRMs have an identical chemical subgroup structure in place consisting of a dimethyl-amino phenyl group that is subject to metabolic oxidation reactions resulting in the formation of aniline derivatives (see Fig. 5) [17–19]. Aniline derivatives have been reported to represent a ‘structural alert’ and could cause undesired liver effects by the formation of reactive intermediates [14, 20, 21] in rare cases, if common detoxification mechanism, for example via glutathione adduct formation or other phase II metabolic reactions, fail due to individual constitution. Available data from clinical studies with SPRMs that lack this dimethyl-amino phenyl group, such as vilaprisan and asoprisnil, have provided no evidence for such clinically relevant drug-related change in liver enzyme activity. Therefore, there is a clear differentiation with regard to metabolic pathways and possible metabolic activation between N-dimethylamino phenyl-substituted SPRMs and
vilaprisan [5, 22]. Currently, further detailed mechanistic \textit{in vitro} studies have been initiated, including investigations with liver microsomes, hepatocytes, and cytotoxicity tests under different cell culture conditions to support this hypothesis, and the results from these analyses will be published elsewhere.

### 3.1.5 Population PK Model for Vilaprisan in Premenopausal Women

A population PK meta-analysis showed that the PK of vilaprisan can be described by a linear two-compartment model with first-order elimination from the central compartment and first-order absorption kinetics including a lag time [23]. This population PK analysis was based on the PK data obtained in premenopausal or perimenopausal women between 21 and 50 years of age in two phase I [24, 25] and two phase II studies (ASTEROID 1 and ASTEROID 2 trials) [26, 27] as described in detail by Sutter et al. [23]. The results from the population PK model were consistent with the dense PK data established initially in postmenopausal women. Furthermore, no difference in PK was observed between healthy participants and patients.

Among a number of potentially relevant demographic covariates, the covariates body weight and body mass index (BMI) were identified as having a statistically significant effect on the apparent volume of distribution of the central compartment (V2/F) and apparent clearance (CL/F), respectively. The increase in V2/F with body weight was allometrically scaled.

The CL/F estimate for non-obese subjects (BMI < 30 kg/m²) was 13.4 L/h, which was 77.3% of the value for obese subjects (BMI ≥ 30 kg/m²), suggesting slightly higher systemic exposure in obese subjects. This would be consistent with the hypothesis that morbidly obese individuals are under chronic inflammation conditions, leading to the suppression of CYP3A4 activity [28]. Overall, both covariates, i.e., body weight and BMI, are not considered clinically relevant for vilaprisan as they explain < 5% of the observed variability in the PK of vilaprisan. Further evaluations are warranted that include data from phase III studies to substantiate the findings of the covariate analysis reported by Sutter et al. [23]. The current database (N = 414 subjects) was too small for an extensive covariate analysis, and also too homogenous as it included mainly Caucasians (70.8%; 13.8% Asians, 12.6% Blacks or African Americans).

### 3.2 Impact of Intrinsic and Extrinsic Factors on the PK of Vilaprisan

#### 3.2.1 Overview

The impact of various intrinsic and extrinsic factors on the exposure of vilaprisan was tested in a number of dedicated phase I studies. In addition, a few preselected potential impact factors were tested as covariates during the development of the above-described population PK model for vilaprisan [23]. An overview of the results of these studies and analyses is given in Table 2. Details are discussed in the subsequent sections.

#### 3.2.2 Intrinsic factors

**3.2.2.1 Age and Menopausal State** No major impact of age and menopausal state (pre- or postmenopausal) on vilaprisan exposure was detected. Furthermore, neither was age identified as a significant covariate in the population PK meta-analysis of data obtained in 414 premenopausal women between 21 and 50 years of age [23], and nor were there any marked differences in vilaprisan exposure between healthy postmenopausal women, who were mostly...
| Potential impact factor | Observed impact on VPR exposure | Comments and recommendations |
|-------------------------|---------------------------------|-------------------------------|
| **Intrinsic factors**   |                                 |                               |
| Age and menopausal state| No relevant impact              | Age and menopausal state were not identified as significant covariates in the population PK meta-analysis by Sutter et al. [23].<sup>a</sup> |
| Sex                     | No relevant impact              | No relevant differences in the PK of VPR were seen between male and female subjects [30].<sup>b</sup> |
| Body size               | No relevant impact              | Body weight was identified as a significant covariate for the apparent peripheral volume of distribution, and body mass index was identified as a significant covariate for the apparent clearance of VPR [23].<sup>a,c</sup> The two covariates explained only a small fraction of the observed parameter variability (1.2% and 4.4%, respectively). Thus, no dose adjustment based on body size is necessary. |
| Ethnicity and race      | Probably no relevant impact     | ‘Racial category’ (Caucasian vs. non-Caucasian; Black vs. non-Black, etc.) was not identified as a significant covariate in the population PK analysis by Sutter et al. [23].<sup>a</sup> Furthermore, largely the same VPR exposure was observed in studies with Chinese, Japanese, and mainly Caucasian/White postmenopausal subjects (ESM 3). No dose adjustment based on race or ethnicity is necessary. |
| Renal impairment        | Increase                        | VPR exposure was mildly increased in subjects with moderate renal impairment (eGFR 30–59 mL/min/1.73 m²) compared with healthy controls (estimated AUC ratio 135%) [29]. No dose adjustment is required for these patients. Based on only limited data in subjects with severe renal impairment, VPR is not recommended to be used in this patient population. |
| Hepatic impairment      | Increase                        | Only mild increases of < 1.75-fold in exposure were observed in subjects with mild (Child–Pugh A) or moderate (Child–Pugh B) hepatic impairment compared with control subjects [30]. No dose adjustment is required in patients with mild or moderate hepatic impairment. Use of VPR in patients with severe hepatic impairment is not recommended. |
| Uterine fibroids        | No relevant impact              | The exposure values estimated for premenopausal women with uterine fibroids were similar to those determined in healthy postmenopausal women (ESM 3). |
| **Extrinsic factors**   |                                 |                               |
| Concomitant food intake | No relevant impact              | AUC was slightly increased in the fed vs. fasted state (+ 20%) and C<sub>max</sub> was slightly reduced (− 11%) [13]. This difference is not clinically relevant and no specific recommendations on how to take VPR (i.e., with or without a meal) are required. |
| Concomitant intake of a strong CYP3A4 inhibitor (itraconazole) | Increase | Pre- and coadministration of itraconazole (200 mg/day) increased VPR exposure AUC<sub>11d</sub> by approximately 6.2-fold and C<sub>max</sub> by approximately 1.8-fold [11]. Concomitant use of VPR with strong CYP3A4 inhibitors, such as itraconazole, is not recommended. |
| Concomitant intake of a strong CYP3A4 inducer (rifampicin) | Decrease | Pre- and coadministration of rifampicin (600 mg/day) decreased VPR exposure by approximately 96% and C<sub>max</sub> by approximately 86% [32]. Concomitant use of VPR with strong CYP3A4 inducers, such as rifampicin, is not recommended. |
| Concomitant intake of a combined oral contraceptive | No relevant impact | Concomitant intake of a combined oral contraceptive mildly increased VPR exposure (estimated AUC ratio 112%; 90% CI 102–122%) [33]. Of note, VPR had no effect on the exposure of EE or LNG, but it interfered with the pharmacodynamic effects of the contraceptive. Thus, it is not recommended to combine oral contraceptives and VPR. |

AUC area under the concentration–time curve, C<sub>max</sub> maximum observed concentration, CI confidence interval, CYP cytochrome P450, EE ethinylestradiol, eGFR estimated glomerular filtration rate, LNG levonorgestrel, PK pharmacokinetic(s), VPR vilaprisan

<sup>a</sup>Data obtained in premenopausal women

<sup>b</sup>Data obtained in postmenopausal women

<sup>c</sup>Other body size parameters tested as potential covariates were fat-free body mass and fat mass
3.2.2.2 Sex No major impact of sex on vilaprisan exposure was detected. Due to the currently targeted indications, i.e., UFs and endometriosis, almost all studies with vilaprisan were conducted in women. Men were included in only two studies—a PK study in patients with renal impairment [29] and a PK study in patients with hepatic impairment [30]. A subgroup analysis within the latter study did not reveal any obvious differences in the vilaprisan exposure levels of men and women with normal hepatic function.

3.2.2.3 Body Size As mentioned above, two covariates were identified—body weight as a significant covariate for V2/F and BMI as a significant covariate for CL/F; they explained 1.2% and 4.4% of the V2/F and CL/F variability, respectively [23]. Thus, no dose adjustment based on body size is necessary.

The CL/F estimate for non-obese subjects (BMI < 30 kg/m²) was 13.4 L/h; for obese subjects (BMI ≥ 30 kg/m²), the CL/F estimate was only 77.3% of that value. This finding is not unexpected: lower clearance in obese individuals than in non-obese individuals has also been reported for other CYP3A4 substrates [31].

3.2.2.4 Ethnicity and Race No major impact of ethnicity or race on the PK of vilaprisan was detected. Furthermore, neither was ‘racial category’ identified as a significant covariate in the population PK analysis [23], and nor were there any major differences in vilaprisan exposure between the mainly Caucasian, Chinese, and Japanese populations studied in phase I studies of vilaprisan [10, 12] (ESM 2). However, as mentioned above, the number and racial and ethnic diversity of the patients included in the phase I and II studies was limited. Data from phase III studies with a larger sample size and focus on the exposure–response relationships are needed to conclusively assess the impact of race and ethnicity on the PK and, finally, the efficacy of vilaprisan. This question is of particular relevance because epidemiologic studies have shown that the prevalence of UFs is markedly higher in Black women than in White women [2, 3].

3.2.2.5 Renal Impairment A study in patients with moderate or severe renal impairment (estimated glomerular filtration rate [eGFR] 30–59 mL/min/1.73 m² and < 30 mL/min/1.73 m², respectively) and matched healthy control subjects showed that the exposure of vilaprisan is very similar in individuals with impaired renal function and individuals with normal renal function [29]. The geometric mean AUC of vilaprisan was increased by a factor of 1.35 in participants with moderate renal impairment compared with healthy controls (90% confidence interval [CI] 0.918–1.973). The geometric mean CL/F was 9.3 L/h (CV 62.1%; N = 9) in moderately impaired subjects and 12.5 L/h (CV 31.9%; N = 9) in healthy controls. The CL/F observed in severely impaired subjects was very similar to the latter value (12.4 L/h; CV 63.5%; N = 3). There were no obvious correlations between eGFR and any of the PK parameters studied.

Overall, these findings are as expected for a drug that is eliminated from plasma almost completely by hepatic metabolism. Based on these data, no dose adjustment is required for patients with mild or moderate renal impairment, and the ‘standard’ 2 mg dose chosen for phase III studies [23] can also be used in this patient population. However, due to lack of sufficient data, it is not recommended to use vilaprisan in patients with severe renal impairment.

3.2.2.6 Hepatic Impairment A study in patients with mild or moderate hepatic impairment (Child–Pugh A or B) and matched healthy control subjects showed that the exposure of vilaprisan is increased in patients with hepatic impairment [30], as expected for a compound that is mainly metabolized by the liver through oxidative and reductive metabolism.

Unbound vilaprisan exposure was 1.44-fold higher in patients with mild hepatic impairment than in healthy controls (90% CI 0.91–2.26) and 1.74-fold higher in patients with moderate impairment (90% CI 1.09–2.78). The maximum observed peak concentrations of unbound vilaprisan were similar in patients with hepatic impairment and healthy controls. There was a moderate positive correlation between AUC₀ₚ and bilirubin level (r = 0.5593) and a moderate negative correlation between AUC₀ₚ and albumin (r = −0.4568).

Overall, the observed impact of hepatic impairment on vilaprisan exposure was mild. Thus, adjustment of the vilaprisan dose is not considered necessary for patients with mild or moderate hepatic impairment. Due to missing data, vilaprisan is not recommended to be used in patients with severe hepatic impairment.

3.2.2.7 Uterine Fibroids The vilaprisan exposure estimates for participants of the ASTEROID trials, i.e., premenopausal women with UFs and heavy menstrual bleeding, are similar to the values determined in healthy postmenopausal women (ESM 3).
3.2.3 Extrinsic Factors/Interaction Potential

3.2.3.1 Concomitant Food Intake  Food intake has a negligible impact on the PK of vilaprisan. In a food–drug interaction study [13], the extent of absorption (as reflected in the AUC) was increased by approximately 20% when vilaprisan was taken at the end of a high-fat/high-calorie or moderate-fat/moderate-calorie meal compared with fasted conditions. On the other hand, the rate of absorption was slightly decreased (Cmax reduced by approximately 10%) and the time to Cmax increased from 1.5 to 4 h. These differences are not clinically relevant and thus no specific recommendations are made on whether to take vilaprisan on an empty stomach or with a meal are required.

3.2.3.2 Concomitant Drug Intake/Drug–Drug Interactions with Vilaprisan as the Victim  CYP3A4 was identified as the predominant CYP isoform responsible for oxidative phase I biotransformation reactions of vilaprisan in in vitro studies. Aldoketoreductase (AKR) contributes to vilaprisan metabolism to a lower extent; therefore, the risk of clinically relevant DDIs with vilaprisan as a substrate of CYP3A4 has been confirmed in two clinical interaction studies. Concomitant administration of CYP3A4 inhibitors or inducers has a substantial impact on the PK of vilaprisan. In a PK DDI study with the CYP3A4 inhibitor itraconazole, pre- and coadministration of itraconazole (200 mg/day) increased the vilaprisan exposure approximately 6.2-fold and Cmax approximately 1.8-fold [11]. In another DDI study, pre- and coadministration of the CYP3A4 inducer rifampicin (600 mg/day) decreased vilaprisan exposure by approximately 96% and Cmax by about 86% [32]. Therefore, concomitant use of vilaprisan with strong CYP3A4 inhibitors or inducers is not recommended.

Vilaprisan is classified as a highly permeable compound. It was identified as a P-glycoprotein (P-gp) substrate but shows no substrate characteristics towards breast cancer resistance protein (BCRP) or the hepatic uptake transporters organic anion transporting polypeptides (OATP) IB1, OATP1B3, and organic cation transporter (OCT) 1.

As vilaprisan is hardly eliminated as an unchanged compound via excretion into feces and/or urine, it is considered unlikely that coadministration of a potent P-gp inhibitor will affect the clearance pathways of vilaprisan. Vilaprisan was also identified as a highly permeable compound, and efflux transporters, such as P-gp, are believed to be less important for the absorption of substrates that are highly permeable. Subsequent clinical data from the DDI study with the strong CYP3A4 and P-gp inhibitor itraconazole supported this assumption, as the time to reach Cmax (tmax) of vilaprisan was not shortened in the presence of itraconazole, which would have been expected if P-gp is relevantly involved in the efflux of vilaprisan during the absorption phase.

Concomitant intake of a combined oral contraceptive with vilaprisan mildly increased vilaprisan exposure (estimated AUC ratio 112%; 90% CI 102–122%) [33].

4 Pharmacodynamic (PD) Properties and PK/PD Relationships

4.1 PD in Healthy Premenopausal Women

In healthy premenopausal women, multiple daily doses of vilaprisan (0.1–5 mg) resulted in a dose-dependent amenorrhea rate (spotting allowed) during the 3-month treatment period. The maximum amenorrhea rate was reached after vilaprisan 2 mg, with a point estimate of 93% (90% credible interval 83–98%) without a clear further increase after higher dosages [24]. After the end of treatment, menstrual bleeding returned within 20.3–25.8 days. In a further PD study in healthy premenopausal women, daily oral administration of vilaprisan at doses of 0.5, 1, 2 or 4 mg over 84 days was investigated. Vilaprisan effectively and dose-dependently inhibited ovulation in more than 80% of women receiving vilaprisan at dosages of ≥ 1 mg/day [25]. After the end of treatment, ovulatory cycles returned quickly, as evidenced by growing follicles and increased estradiol (E2) values followed by follicle rupture and rise of progesterone values. Although vilaprisan effectively inhibited ovulation, the development of active follicle-like structures was not suppressed under treatment. Maximum follicle sizes were slightly increased during treatment across all dose groups (Fig. 6). At follow-up, values were similar to those measured in the pretreatment cycle. No persistent follicles/ovarian cysts of critical size were observed.

E2 levels were moderately decreased during treatment with vilaprisan; however, mean average E2 concentrations remained above 80 pg/mL in line with the development of follicles. The decrease in E2 levels was fully reversible after the end of treatment.

As vilaprisan has an embryo-lethal effect in rats and rabbits, patients are required to use an acceptable non-hormonal method of contraception (e.g., condom with spermicide) during treatment with vilaprisan (see also Sect. 5.2).

2 Ovarian activity was classified according to Hoogland and Skouby (Contraception. 1993;47(6):583–590). Three parameters determining ovarian activity are combined to a 6-step scoring system: (a) the diameter of the maximum follicle-like structure; (b) the E2 serum concentration; and (c) the progesterone serum concentration. Ovulation inhibition was defined as Hoogland score < 6 in the complete treatment epoch.

3 Follicle size was measured by transvaginal ultrasound, and E2, progesterone, and follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels were determined repeatedly before, during, and after treatment [25].

△ Adis
4.2 PD in Premenopausal Women with Uterine Fibroids

4.2.1 Induction of Amenorrhea

The amenorrhea rates observed in premenopausal women with symptomatic UFs treated with different doses of vilaprisan [26, 27] increased in a similar dose-dependent manner as those described above for healthy premenopausal women. In the ASTEROID 1 trial, for example, amenorrhea was achieved in the majority of subjects after a few days of treatment with vilaprisan 1, 2, or 4 mg/day and maintained until the end of treatment in week 12 (cumulative amenorrhea rate 85%, 89%, and 83%, respectively) [26].

A recently published exposure–response analysis of the data from this trial shows a steep exposure–response relationship for induced amenorrhea (Fig. 7) [23]. The estimated maximum probability of inducing amenorrhea (maximum achievable response rate) was 59% (95% CI 49–68), with an AUC$_{24}$ at steady state (AUC$_{24ss}$) of 36.9 μg·h/L (95% CI 27.7–48.7). Simulations showed that an exposure resulting in 90% of the maximum probability of inducing amenorrhea will be reached by 98% of patients with once-daily administration of vilaprisan 2 mg, while this threshold will be reached by only 64% of patients at 1 mg/day. Therefore, the 2 mg dose was chosen for phase III studies in patients with UFs.

Graphical comparisons of simulated and observed probability for amenorrhea showed that the exposure–response relationship based on ASTEROID 1 was consistent with ASTEROID 2 data. A covariate analysis of the relationship between vilaprisan exposure and induction of amenorrhea did not reveal any statistically significant differences between different racial subgroups and the overall population. However, as mentioned before with regard to vilaprisan exposure, the sample used for this analysis was not large enough to allow qualified conclusions about factors potentially impacting the PD of vilaprisan.
4.2.2 Reduction of Estradiol Levels

As a safety parameter, exposure of unbound E2 during treatment with vilaprisan was investigated. In the ASTEROID 1 and 2 trials, the concentrations of unbound E2 were mostly within the physiologic range for the follicular phase during treatment with vilaprisan, although a moderate trend toward lower E2 levels with increasing vilaprisan exposure was observed [26]. An exposure–response analysis for E2 concentrations in serum confirmed this observation [23], as shown in Fig. 8. The clinical relevance of the decrease in E2 levels cannot be assessed based on the available vilaprisan short-term phase II data and should be further evaluated in long-term safety studies.

4.3 QTc-Prolongation Potential

Critical evaluations of the electrocardiogram data obtained in clinical studies with vilaprisan did not suggest a risk for QT prolongation following administration of vilaprisan,
and neither are any such class effects known for SPRMs. However, as it is possible that vilaprisan concentrations markedly above the expected therapeutic range are reached when the drug (against the recommended use) is taken together with a strong CYP3A4 inhibitor [11], an integrated vilaprisan concentration–QTc response analysis across all available studies with triplicate electrocardiogram measurements and corresponding PK data was conducted (ESM 4). As illustrated in Fig. 9, there are no indications that the mean difference in QTc intervals from baseline and placebo ($\Delta \Delta$QTc) exceeds 10 ms at systemic exposures up to 193 µg/L—a concentration that is approximately 17-fold above the maximum concentration observed after multiple administration of the intended therapeutic dose of 2 mg, i.e., even if a strong CYP3A4 inhibitor such as itraconazole is taken concomitantly, there appears to be no risk for QTc prolongation.

5 Interaction Potential

5.1 PK Interactions

As already described above, two dedicated DDI studies with vilaprisan as the victim of CYP3A inducers and inhibitors were conducted during the development of the drug. In contrast, interaction studies with vilaprisan as the perpetrator were not conducted.

Since no inhibition of CYP enzymes was observed up to 5 µM vilaprisan concentrations with CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 in in vitro assays, the risk for clinically relevant DDIs of vilaprisan with substrates of these enzymes is considered to be low. Furthermore, there is no potential of induction of CYP3A4 activity when taking the maximum unbound plasma concentration at a dose of 4 mg/patient into account.

Uridine 5′-diphospho-glucuronosyltransferase (UGT) 1A4 and UGT1A1 were moderately inhibited by vilaprisan, with IC$_{50}$ values of 26.6 and 11.4 µM, respectively. No inhibition of UGT1A6, 1A9, 2B4, and 2B7 was observed. Maximum unbound concentration of
an anticipated maximum therapeutic dose of 4 mg/day in the endometriosis indication is predicted to be about 2 nmol/L, which is >2000-fold lower than the maximum tested concentrations of 5 µM that showed no inhibitory effect. Therefore, the risk for clinically relevant DDIs with vilaprisan as the perpetrator and comediations that are substrates of these enzymes is considered to be low. Vilaprisan is no inhibitor for P-gp, BCRP, OATP1B1, OATP1B3, OCT1, or the renal uptake transporters OAT1, OAT3, and OCT2 as well as MATE1 and MATE2K and BSEP, investigated in appropriate in vitro assays (data on file, Bayer AG) [ESM 5].

Fig. 9 Relationship between vilaprisan plasma concentration and QTc interval. The numbers starting with ‘14…’ are study numbers. The symbols in the upper graph show the mean of the observed ΔΔQTcF for each concentration bin; the vertical lines show the 90% CIs of the mean; and the solid line is the predicted typical change in ΔΔQTcF with increasing vilaprisan plasma concentrations. The gray area shows the predicted 90% CI; the long dashed (blue) line shows the $C_{\text{max,ss}}$ for a 2 mg dose, and the short dashed (blue) line shows the $C_{\text{max,ss}}$ for a 2 mg dose when coadministered with itraconazole 200 mg once daily. The lower graph shows the distribution of the plasma concentrations in different subgroups of subjects as a boxplot. The upper whisker extends from the 75th percentile to the highest value that is within 1.5 × interquartile range, and the lower whisker extends from the 25th percentile to the lowest value within 1.5 × interquartile range. Data beyond the ends of the whiskers are outliers and are plotted as points. The data used for this concentration–response analysis covered a dose range from vilaprisan 0.25 mg administered as a single dose, up to vilaprisan 30 mg/day for 4 weeks. Altogether, 858 paired vilaprisan concentration/QTc values were analyzed using linear mixed-effect modeling. CI confidence interval, $C_{\text{max,ss}}$ maximum concentration at steady state, ΔΔQTc difference in QTc intervals from baseline and placebo.
5.2 PD Interactions

Since many women who suffer from symptomatic UFs are of reproductive age, hormonal contraception is widely used in this patient population. As the progestin component of hormonal contraceptives acts on the PR as an agonist, a PD interaction with SPRMs such as vilaprisan that act predominantly antagonistic on the PR in many tissues must be assumed. In a dedicated clinical PK and PD DDI study with vilaprisan and a combined oral contraceptive consisting of levonorgestrel 0.15 mg and ethinylestradiol 0.03 mg, the known contraceptive-driven suppression of ovarian activity, as assessed using Hoogland scores, was mildly affected by coadministration of vilaprisan [33, 34]. The effects of the contraceptive on cervical function, as assessed using the Insler score [35], was moderately affected when coadministered with vilaprisan, indicating that the efficacy of the contraceptive can no longer be taken for granted. Therefore, the combined use of vilaprisan with oral contraceptives is not recommended.

6 Conclusion

The PK and PD of vilaprisan, an SPRM indicated for the treatment of symptoms associated with UFs and endometriosis, have been extensively characterized in several phase I and II studies, including population PK/PD modeling and physiologically-based PK modeling analyses [36]. A comprehensive evaluation of all generated data covering preclinical in vitro and in vivo investigations up to clinical phase II data led to a thorough understanding of the relevant mechanistic PK and PD processes driving the clinical profile of vilaprisan, and provides a solid basis for practical guidance on the safe and effective use in patients.

Vilaprisan was well tolerated over a broad exposure range, and together with the favorable PK and PD profile, this supports the use of the same dose in all patients irrespective of body weight, race, and age, and also in patients with mild and moderate renally or heptatically impaired function.

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Declarations

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Conflict of interest Marcus-Hillert Schultze-Mosgau, Bart A. Ploeger, Matthias Frei, Joachim Höchel, and Antje Rottmann are employees of Bayer AG.

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Code availability Not applicable.

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