Pharmacokinetics of tibolone in early and late postmenopausal women

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Aims Tibolone is a tissue-specific compound with favourable effects on bone, vagina, climacteric symptoms, mood and sexual well being in postmenopausal women, without stimulating the endometrium or breast. Since tibolone is used for the treatment of both young and elderly postmenopausal women, its pharmacokinetics were studied to investigate potential differences with age. In addition, the bioequivalence of the 1.25 and 2.5 mg tablets was evaluated.

Methods Single doses of 1.25 or 2.5 mg of tibolone were given in a double-blind, randomized, two-way cross-over study to women aged between 45 and 55 years or between 65 and 75 years of age.

Results Age did not have a significant effect on $C_{\max}$, $t_{\max}$, and $t_{1/2}$ of tibolone and its metabolites and on the body weight standardized oral clearance ($CL/F \text{ kg}^{-1}$) of the 3α - and 3β -hydroxy tibolones. In early postmenopausal women, significantly lower values were found for the $AUC(0,16 \text{ h})$, and $AUC(0,\infty)$ of 3α -hydroxy tibolone 24.6 ± 6.6 vs 29.2 ± 4.9 and 27.1 ± 6.9 vs $32.3 \pm 6.5 \text{ ng ml}^{-1} \text{ h}$ for the 1.25 mg tablet, respectively, and 45.4 ± 13.9 vs 55.7 ± 14.1 and 49.6 ± 14.6 vs $62.6 \pm 17.3 \text{ ng ml}^{-1} \text{ h}$ for the 2.5 mg tablet, respectively. When these values were adjusted for the significantly higher body weight of the early postmenopausal women, the differences disappeared. No significant differences between early and late postmenopausal women were found for the $AUC(0,8 \text{ h})$, and $AUC(0,\infty)$ of 3β -hydroxy tibolone. The rate of absorption of tibolone and the rates of absorption or formation of the 3α - and 3β -hydroxy tibolones were significantly higher after the 1.25 mg dose than after the 2.5 mg tablet, resulting in increases of 32%, 27% and 17% for the dose normalized- $C_{\max}$ of tibolone and the 3α - and 3β -hydroxy tibolones, respectively. $t_{\max}$ for tibolone and its metabolites was 12–27% less after 1.25 mg compared to 2.5 mg, which was statistically significant. The two formulations were bioequivalent with respect to the dose-normalized $AUC(0,\infty)$ and the $AUC(0,t_{\text{fix}})$ values for the 3α -hydroxy tibolone (ratio point estimate [90%, confidence limits]: 1.08 [1.04, 1.14] and 1.08 [1.03, 1.13], respectively) and for the 3β -hydroxy tibolone (1.07 [1.01, 1.14] and 1.04 [0.96, 1.12], respectively). Both formulations were also bioequivalent with respect to $CL/F \text{ kg}^{-1}$ and $t_{1/2}$.

Conclusions The pharmacokinetics of tibolone are similar in early (age 45–55 years) and late (65–75 years) postmenopausal women. The 2.5 and 1.25 mg tablets are bioequivalent with respect to the extent of absorption. The rate of absorption or formation of the metabolites of tibolone were not bioequivalent, but these differences are considered to have no clinical relevance in view of the chronic administration of tibolone.

Keywords: age, pharmacokinetics, postmenopausal women, tibolone

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Introduction

Tibolone [(7 α , 17 α)-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one] has shown efficacy in treating climacteric symptoms resulting from natural or surgical

menopause and in the prevention of postmenopausal osteoporosis without stimulation of the endometrium or breast [1–4]. Furthermore, in older postmenopausal women evaluated at least 10 years after spontaneous menopause, tibolone produced over a 24 month period a significant increase in bone mineral density in the lumbar spine and distal and ultradistal forearm [2, 5].

Tibolone is rapidly and extensively absorbed following oral administration in healthy postmenopausal women [6] and in animals [7]. It is converted in the intestine and liver to two metabolites, 3α - and 3β -hydroxy tibolone, that are responsible for the oestrogenic effects on bone, vagina and climacteric symptoms [8]. A third metabolite, the Δ^4 -isomer of tibolone has progestagenic and androgenic activities and is also formed in the endometrium [9]. Owing to its rapid metabolism, plasma concentrations of tibolone and of the Δ^4 -isomer quickly fall below the lower limit of quantification. Profiling of the target organs in animals showed a tissue-specific distribution of metabolites, predominantly in their sulphated form [7].

Despite the use of tibolone in older postmenopausal women, its pharmacokinetics in this patient subpopulation have not been previously reported. The objectives of this study were: (1) to compare the pharmacokinetics of tibolone and its metabolites, following administration of tibolone 1.25 mg and 2.5 mg tablets, in early (45–55 years of age) *vs* late (65–75 years of age) postmenopausal women, and (2) to test the relative bioequivalence of the two formulations of tibolone after single oral administration of 1.25 mg and 2.5 mg to early and late postmenopausal women.

Methods

This was a single-centre study, conducted at Aster, 3–5 Rue Eugène, Millon (75015 Paris, France). The study was approved by the Ethics Committee of La Pitié-Salpêtrière, Division Saint-Vincent and written informed consent was obtained before subject enrolment.

Subjects

Thirty-two healthy women (16 early postmenopausal, subset A, and 16 late postmenopausal, subset B) participated. Subjects were between 45 and 55 years of age (subset A) or between 65 and 75 years of age (subset B), with a body mass index ≥ 20 and ≤ 28 kg m⁻². Subjects had normal mental health and were postmenopausal, i.e. at least 6 months had elapsed after the last natural menstrual bleeding and serum follicle stimulating hormone (FSH) concentrations were greater than 40 IU l⁻¹ and oestradiol concentrations less than 20 pg ml⁻¹.

Women were not enrolled in the study if they had clinically significant abnormalities in the results of the following tests: cervical smear, mammography, haematological or biochemical values at screening, serum liver enzyme concentrations (ALAT, ASAT, and γ -GT), physical examination, electrocardiogram, or blood pressure (systolic blood pressure > 170 mmHg and/or diastolic blood pressure > 105 mmHg). Additional exclusion criteria were a history or presence of hepatic or renal disease, epilepsy or migraine (requiring drug treatment), cardiovascular or cerebrovascular disease, thromboembolism, or thrombosis. Also excluded were women with positive serology for hepatitis B, hepatitis C, or HIV, or those who had taken oral oestrogen and/or progestin therapy within the 2 months preceding the study, used transdermal hormone therapy within 1 month of the study, received hormone injections within 6 months of the study, or had hormone implants at any time previously. Other exclusion criteria consisted of the following: history or presence of malignancy, type I or II diabetes mellitus, alcohol and/or drug abuse in the last 3 months and/or positive alcohol/drug screening, known hypersensitivity or contraindication to oestrogen and/or progestins, participation in a drug study or blood donation within the 90 days prior to the study, smoking within the last 6 months, or poor venous accessibility. No other medications, besides tibolone, were allowed from 8 days prior to the study and until its completion.

Study design

This was a double-blind, randomized, two-way cross-over trial in which subjects were randomized to receive a single oral dose of tibolone 1.25 mg or 2.5 mg on day 1. Following a washout period of 7 days, subjects received the other dose on day 8. Subjects were housed in the clinical research unit from the afternoon of day –1 until the morning of day 2 and from the afternoon of day 7 until the morning of day 9. Tibolone was administered to subjects in the fasting state at approximately 08:00 h on days 1 and 8. Blood samples were obtained prior to and 30 min, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 20, and 24 h after the administration of each dose.

Safety parameters

During the pharmacokinetic study, the safety and tolerability of tibolone were also assessed. Vital signs were measured at the screening examination and on days 1, 2, 7, 8, and 9. Physical examinations and laboratory analyses (i.e. blood chemistry and haematology) were performed at the screening examination and on day 9. Recording of adverse events was ongoing throughout the study period.

Drug analysis

Plasma concentrations of tibolone, Δ^4 -isomer, 3α - and 3β -hydroxy tibolone were measured by gas chromatographic mass spectrometry (GC-MS) as described elsewhere [7]. The assays for tibolone and the Δ^4 -isomer were performed after extraction with n-hexane. The lower limit of quantification for both tibolone and the Δ^4 -isomer was 0.1 ng ml^{-1} . At this concentration, the accuracy and precision were 105% and 10%, respectively, for tibolone and 94% and 20%, respectively, for Δ^4 -isomer. The GC-MS assays for 3α - and 3β -hydroxy tibolones were performed with sample purification using solid phase extraction followed by derivatization with Tri-Sil[®] reagent and n-hexane extraction. The lower limit of quantification for both 3α - and 3β -hydroxy tibolones was 0.1 ng ml^{-1} . At this concentration, the accuracy and precision were 102% and 8%, respectively, for the 3α -hydroxy metabolite and 104% and 10%, respectively, for the 3β -hydroxy metabolite.

Pharmacokinetic parameters

Pharmacokinetic parameters were calculated by noncompartmental methods. Pharmacokinetic measurements for tibolone and its Δ^4 -isomer included the maximum concentration of drug in plasma ($C_{\max}$) and the time at maximum concentration of drug in plasma ($t_{\max}$). Those for 3α - and 3β -hydroxy tibolones included $C_{\max}$, $t_{\max}$, the area under the plasma concentration-time curve from time 0 to t_{fix} , defined as the last common time point for which all subjects had measurable ($\geq$ lower limit of quantification) concentrations ($\text{AUC}(0, t_{\text{fix}})$) and its dose-normalized value ($\text{dn-AUC}(0, t_{\text{fix}})$), the area under the plasma concentration-time curve from time 0 to infinity ($\text{AUC}(0, \infty)$), its dose-normalized value ($\text{dn-AUC}(0, \infty)$), the oral clearance per kg body weight ($\text{CL}/F \text{ kg}^{-1}$), and the elimination half-life ($t_{1/2}$).

To test the bioequivalence of tibolone at doses of 1.25 mg and 2.5 mg, the following parameters were analysed for tibolone and its Δ^4 -isomer: the dose-normalized $C_{\max}$ ($\text{dn-}C_{\max}$) and the $t_{\max}$. For 3α - and 3β -hydroxy tibolones: $\text{dn-}C_{\max}$, $t_{\max}$, the dose-normalized $\text{AUC}(0, t_{\text{fix}})$ ($\text{dn-AUC}(0, t_{\text{fix}})$), the dose-normalized $\text{AUC}(0, \infty)$ ($\text{dn-AUC}(0, \infty)$). As additional parameters $\text{CL}/F \text{ kg}^{-1}$; and $t_{1/2}$ were analysed.

$C_{\max}$ and $t_{\max}$ values were noted directly. AUC values were determined by the linear trapezoidal rule. Dose-normalized values for $C_{\max}$ and AUC were calculated as the quotient of $C_{\max}$ and dose and of AUC and dose, respectively. The value of $\text{CL}/F \text{ kg}^{-1}$ was calculated as dose divided by $\text{AUC}(0, \infty)$ and standardized to body weight. $t_{1/2}$ was calculated according to the equation, $t_{1/2} = 0.693/\lambda_z$, where λ_z is the slope of the terminal

log-linear phase of the concentration *vs* time curve obtained by log-linear regression.

Statistical procedures

Descriptive statistics were used to summarize the demographic data. No distinction was made between sequence groups. For the pharmacokinetic parameters, mean values and their standard deviations were calculated for the early and the late postmenopausal subjects and for each formulation (i.e. 1.25 mg and 2.5 mg). For all parameters, differences between the means of early and late postmenopausal subjects were tested for significance using an ANOVA on the log-transformed (base e) values.

For bioequivalence testing purposes, the 1.25 mg tablet served as the test formulation and the 2.5 mg tablet as the reference formulation. For all parameters, point estimates and their 90% parametric confidence intervals derived from analysis of variance (ANOVA) on log-transformed (base e) values for the true test-to-reference ratio were calculated. The data were subjected to ANOVA with a consideration for the following factors, age, sequence (order of treatment), period (time of treatment) and dose.

To our knowledge, no statistical procedure is available to calculate the 90% nonparametric confidence intervals for $t_{\max}$ for our present study design. Therefore, we have chosen to deviate from the usual procedure to apply a nonparametric analysis for $t_{\max}$ and, instead, we have calculated the ratio and the parametric 90% confidence limits.

The two formulations were declared bioequivalent with respect to a given parameter if the 90% confidence interval was fully contained within the acceptance range of 0.80–1.25. All pharmacokinetic calculations were performed using SAS software.

Results

Demographic data for the subjects are presented in Table 1. Subjects in the early postmenopausal group were significantly ($P < 0.05$) younger, taller, and heavier than those in the late postmenopausal group. All 32 subjects completed the study. However, data from one subject in the late postmenopausal group were not included in the pharmacokinetic evaluation ($n = 31$) because her plasma concentrations of tibolone and its metabolites suggested that she inadvertently received 1.25 mg when she was assigned to receive 2.5 mg and *vice versa*. As expected, plasma concentrations of tibolone and its Δ^4 -isomer could only be measured in the circulation during the first 6 h after administration. Hence, the only pharmacokinetic parameters that could be determined for tibolone and the Δ^4 -isomer were $C_{\max}$ and $t_{\max}$.

Figures 1 and 2 show the mean plasma concentration-time curves following administration of tibolone 1.25 mg and 2.5 mg in early and late postmenopausal subjects for 3α - and 3β -hydroxy tibolone, respectively. Table 2 provides a summary of the pharmacokinetic parameters for tibolone, its Δ^4 -isomer and the 3α - and 3β -hydroxy tibolones. The last time point for which all subjects had measurable concentrations (t_{fix}) of 3α - and 3β -hydroxy

Table 1 Subject demographics (mean $\pm$ s.d.).

Subset	Age (years)	Height (cm)	Weight (kg)
Early postmenopausal ($n = 16$)	52.6 ± 2.0^a	164.9 ± 5.3^a	65.5 ± 6.3^a
Late postmenopausal ($n = 15$)	68.1 ± 2.8	156.7 ± 6.5	58.5 ± 5.4

^a $P < 0.05$, early *vs* late postmenopausal women (*t*-test for unequal variances).

Figure 1 Plasma concentration-time profiles for 3α -hydroxy tibolone following administration of tibolone, 1.25 or 2.5 mg, in early and late postmenopausal subjects. $\blacklozenge$ 1.25 mg early, $\blacksquare$ 1.25 mg late, $\blacktriangle$ 2.5 mg early, $\circ$ 2.5 mg late.

Figure 2 Plasma concentration-time profiles for 3β -hydroxy tibolone following administration of tibolone, 1.25 or 2.5 mg, in early and late postmenopausal subjects. $\blacklozenge$ 1.25 mg early, $\blacksquare$ 1.25 mg late, $\blacktriangle$ 2.5 mg early, $\circ$ 2.5 mg late.

tibolone was 16 h and 8 h, respectively. Because of the absence of a log-terminal linear phase in plasma concentration-time plots of 3β -hydroxy tibolone following administration of tibolone 1.25 mg, $t_{1/2}$ could not be estimated in seven subjects. Consequently, $\text{AUC}(0, \infty)$ and $\text{CL}/F \text{ kg}^{-1}$ could not be calculated for these subjects.

Except for the $\text{AUC}(0, 16 \text{ h})$ and $\text{AUC}(0, \infty)$ values for 3α -hydroxy tibolone at both tibolone doses, no statistically significant age effects were found. Mean dose-normalized $\text{AUC}(0, 16 \text{ h})$ and $\text{AUC}(0, \infty)$ values for the 3α -hydroxy tibolone were both 19% lower for the 1.25 mg and 2.5 mg doses in the younger group compared with the older group.

The results of bioequivalence testing are summarized in Table 3. Except for the Δ^4 -isomer, the two tibolone formulations (1.25 mg and 2.5 mg) were not bioequivalent with respect to the rate of absorption of tibolone and the rate of formation of 3α - and 3β -hydroxy tibolone, as characterized by dose-normalized C_{max} and t_{max} . Specifically, dose-normalized C_{max} values were higher (32% for tibolone, 27% for 3α -hydroxy tibolone, and 17% for the 3β -hydroxytibolone) after the 1.25 mg tablet. However, the two tibolone formulations were bioequivalent with respect to the extent of formation of 3α - and 3β -hydroxy tibolone, as characterized by the dose-normalized $\text{AUC}(0, \infty)$ and $\text{AUC}(0, t_{\text{fix}})$ values.

No clinically significant changes occurred between examination at screening and at study completion with respect to vital signs, physical status, and laboratory parameters. Mild to moderate headaches were reported by 12 subjects (6 in the early postmenopausal group and 6 in the late postmenopausal group). Mild to moderate hot flushes were reported on two occasions by two subjects in the early postmenopausal group. Another early postmenopausal subject complained of mild acne. Other adverse effects reported by one subject each in the late postmenopausal group included: nausea, sleepiness and vomiting. All adverse effects were well-tolerated and resolved spontaneously without sequelae.

Discussion

The results obtained in this study showed that age did not influence the disposition of tibolone and its metabolites. Significant differences in the pharmacokinetics of tibolone and its metabolites in early *vs* late postmenopausal groups were only found for the $\text{AUC}(0, 16 \text{ h})$, and $\text{AUC}(0, \infty)$ of 3α -hydroxy tibolone. A likely explanation for this finding is the higher body weight of the early postmenopausal women. If the oral clearance is normalized to body weight ($\text{CL}/F \text{ kg}^{-1}$), no significant age-related difference in apparent clearance remains (i.e. $0.74 \text{ vs } 0.70 \text{ l h}^{-1} \text{ kg}^{-1}$ for the 1.25 mg dose and $0.83 \text{ vs } 0.75 \text{ l h}^{-1} \text{ kg}^{-1}$ for the 2.5 mg dose).

Table 2 Pharmacokinetic parameters (mean $\pm$ s.d.) for tibolone and its metabolites in early and late postmenopausal women.

Compound measured	Parameter	Tibolone 1.25 mg		Tibolone 2.5 mg	
		Early	Late	Early	Late
Tibolone	$C_{\max}$ (ng ml ⁻¹)	0.9 $\pm$ 0.3	1.1 $\pm$ 0.4	1.5 $\pm$ 0.7	1.6 $\pm$ 0.8
	$t_{\max}$ (h)	1.0 $\pm$ 0.7	0.9 $\pm$ 0.7	1.3 $\pm$ 0.7	1.1 $\pm$ 0.6
Δ^4 -isomer	$C_{\max}$ (ng ml ⁻¹)	0.3 $\pm$ 0.1	0.3 $\pm$ 0.1	0.4 $\pm$ 0.2	0.8 $\pm$ 1.1
	$t_{\max}$ (h)	1.6 $\pm$ 0.8	1.3 $\pm$ 0.8	1.8 $\pm$ 1.4	1.9 $\pm$ 1.3
3 α -hydroxy tibolone	$C_{\max}$ (ng ml ⁻¹)	8.3 $\pm$ 2.9 ^a	10.9 $\pm$ 3.3	14.6 $\pm$ 5.4	16.7 $\pm$ 6.6
	$t_{\max}$ (h)	1.2 $\pm$ 0.7	0.9 $\pm$ 0.7	1.3 $\pm$ 0.6	1.3 $\pm$ 0.6
	AUC(0,16 h) (ng ml ⁻¹ h)	24.6 $\pm$ 6.6 ^a	29.2 $\pm$ 4.9	45.4 $\pm$ 13.9 ^a	55.7 $\pm$ 14.1
	AUC(0, ∞) (ng ml ⁻¹ h)	27.1 $\pm$ 6.9 ^a	32.3 $\pm$ 6.5	49.6 $\pm$ 14.6 ^a	62.6 $\pm$ 17.3
	CL/F kg ⁻¹ (l h ⁻¹ kg ⁻¹)	0.74 $\pm$ 0.15	0.70 $\pm$ 0.17	0.83 $\pm$ 0.2	0.75 $\pm$ 0.25
3 β -hydroxy tibolone	$t_{1/2}$ (h)	6.4 $\pm$ 1.0	5.9 $\pm$ 1.6	5.7 $\pm$ 0.6	6.0 $\pm$ 1.2
	$C_{\max}$ (ng ml ⁻¹)	2.1 $\pm$ 0.6	2.1 $\pm$ 0.8	3.8 $\pm$ 1.4	3.7 $\pm$ 2.0
	$t_{\max}$ (h)	1.4 $\pm$ 0.6	1.2 $\pm$ 0.6	1.6 $\pm$ 0.9	1.5 $\pm$ 0.8
	AUC(0,8 h) (ng ml ⁻¹ h)	6.2 $\pm$ 1.8	5.7 $\pm$ 1.4	11.7 $\pm$ 3.6	10.9 $\pm$ 2.8
	AUC(0, ∞) (ng ml ⁻¹ h)	8.7 $\pm$ 2.2 ^b	8.5 $\pm$ 1.9 ^b	15.9 $\pm$ 4.4	15.5 $\pm$ 4.3
	CL/F kg ⁻¹ (l h ⁻¹ kg ⁻¹)	2.29 $\pm$ 0.41 ^b	2.71 $\pm$ 0.84 ^b	2.58 $\pm$ 0.68	3.04 $\pm$ 1.08
	$t_{1/2}$ (h)	6.2 $\pm$ 2.8 ^b	6.2 $\pm$ 1.3 ^b	6.4 $\pm$ 1.8	5.9 $\pm$ 1.9

$C_{\max}$ = maximum concentration of drug in plasma; $t_{\max}$ = time to maximum concentration of drug in plasma; AUC(0,8 h) and AUC(0,16 h) = area under the plasma concentration-time curve from time 0–8 h or 0 to 16 h, respectively; AUC(0, ∞) = area under the plasma concentration-time curve from time 0 to infinity; CL/F kg⁻¹ = oral clearance per kg body weight; $t_{1/2}$ = elimination half-life; ^a P < 0.05, early vs late postmenopausal women; ^b n = 12; for all other assessments n = 15–16.

Table 3 Bioequivalence testing of the 1.25 and 2.5 mg doses of tibolone.

Parameter	PE	Comparison of 1.25 mg tablet (test) vs 2.5 mg (reference) for tibolone and its metabolites											
		Tibolone			Δ^4 -isomer			3 α -hydroxy tibolone			3 β -hydroxy tibolone		
		90% CI	Res	PE	90% CI	Res	PE	90% CI	Res	PE	90% CI	Res	PE
dn- $C_{\max}$	1.32	1.14, 1.54	NB	1.04	0.91, 1.18	B	1.27	1.15, 1.40	NB	1.17	1.07, 1.28	NB	
$t_{\max}$	0.73	0.59, 0.90	NB	0.79	0.66, 0.94	NB	0.73	0.60, 0.89	NB	0.88	0.73, 1.05	I	
dn-AUC(0, t_{fix})							1.08	1.04, 1.14	B	1.07	1.01, 1.14	B	
dn-AUC(0, ∞)							1.08	1.03, 1.13	B	1.04	0.96, 1.12	B	
CL/F kg ⁻¹							0.92	0.88, 0.97	B	0.96	0.89, 1.04	B	
$t_{1/2}$							1.04	1.00, 1.09	B	1.01	0.91, 1.13	B	

PE: Point estimate of parameter ratio; 90% CI: 90% confidence interval of parameter ratio; Res: Result; (N)B: (not) bioequivalent ((not) bioequivalent means 90% confidence interval (not) contained within 0.80, 1.25); I: indeterminate due to large variation; dn- $C_{\max}$ = dose-normalized maximum concentration of drug in plasma; $t_{\max}$ = time to maximum concentration of drug in plasma; dn-AUC(0, t_{fix}) = dose-normalized area under the plasma concentration-time curve from time 0 to t_{fix} : 16 h for 3 α -hydroxytibolone and 8 h for 3 β -hydroxytibolone; dn-AUC(0, ∞) = dose-normalized area under the plasma concentration-time curve from time 0 to infinity; CL/F kg⁻¹ = oral clearance per kg body weight; $t_{1/2}$ = elimination half-life.

n = 31, except for the following: $C_{\max}$ and $t_{\max}$ of the Δ^4 -isomer (n = 30, because in one subject, all measured plasma concentrations following administration of tibolone 1.25 mg were below the lower limit of quantification) and AUC(0,8 h), AUC(0, ∞), CL/F kg⁻¹, and $t_{1/2}$ of 3 β -hydroxy tibolone (n = 24, because of the absence of a terminal linear phase in subjects' plasma concentration-time plots following administration of tibolone 1.25 mg).

The rate of formation of the Δ^4 -isomer was not significantly different between the two tibolone doses. However, the rate of absorption of the 1.25 mg dose was 32% higher than that of the 2.5 mg dose. Likewise, the rates of formation of 3 α - and 3 β -hydroxy tibolone were 27% and 17% higher, respectively, for the 1.25 mg tablet. Therefore, it is concluded that the 1.25 and 2.5 mg tablets differ with respect to the rate of absorption or the rate of formation of the metabolites. These differences

are unlikely to be of clinical relevance because in practice, tibolone is administered chronically, not as a single dose. More importantly, the two different tibolone formulations were shown to be bioequivalent with respect to the extent of formation of both hydroxy tibolones.

Clinical and biological tolerance of tibolone was good. Only minor adverse effects were reported during the study period. All of these adverse effects resolved spontaneously. Furthermore, no clinically significant changes in vital signs,

physical status, or laboratory test parameters were observed which could be attributed to tibolone. No difference in safety and tolerance was observed between the early and late postmenopausal groups.

In summary, our data demonstrate that age does not have a significant effect on the disposition of tibolone and its metabolites, and the oral clearance (normalized to body weight) of 3α - and 3β -hydroxy tibolones, respectively. The rate of absorption of tibolone and the rates of formation of 3α - and 3β -hydroxy tibolones were significantly higher for the 1.25 mg tablet compared with the 2.5 mg tablet. However, when all subjects were combined the two formulations were bioequivalent with respect to the extent of formation of both metabolites.

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