*Drug Evaluation*

WOMEN'S HEALTH

Women's Health
Volume 16: 1–7

DOI: 10.1177/1745506520957192
journals.sagepub.com/home/whe
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# A single-arm study to evaluate the transfer of drospirenone to breast milk after reaching steady state, following oral administration of 4 mg drospirenone in healthy lactating female volunteers

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## Abstract

**Objective:** The primary objective of this trial was to assess the transfer of drospirenone to breast milk after daily administration of an oral test preparation containing 4 mg of drospirenone at the steady state. The secondary objective of the trial was to assess safety based on clinical and laboratory measurements and reporting of adverse events and/or adverse drug reactions.

**Patients and Methods:** This was an open label, non-comparative single-center study. Drospirenone 4 mg per day was the first postpartum contraceptive for the study participants who were no longer breastfeeding yet were still lactating. It was administered for 7 days to achieve steady-state concentration. All participants were volunteers who planned to use oral contraceptives as their family planning method in the future.

**Results:** Twelve volunteers completed the trial according to the protocol, and the samples of all 12 study completers were analyzed. The average concentration–time curve of drospirenone in plasma 24 h after the administration of the last dose (area under the curve (0–24 h)) was 635.33 ng h/mL and 120 h after the single repeated dose administration (area under the curve (0–120 h)) was 1180.57 ng h/mL, respectively. The average $C_{max}$ was 48.64 ng/mL.

The average concentration–time curve of drospirenone in milk 24 h after the administration of the last dose (area under the curve (0–24 h)) was 134.35 ng h/mL and 120 h after the single repeated dose administration (area under the curve (0–120 h)) was 227.17 ng h/mL, respectively. The average $C_{max}$ was 10.34 ng/mL.

**Conclusion:** On average, 18.13% of plasma drospirenone made it to breast milk and the highest concentration of drospirenone in breast milk was 17.55% of that in plasma. The total quantity of drospirenone passing to breast milk is on average 4478 ng during a 24-h period representing 0.11% of the maternal daily dose. Thus, at the recommended doses, no effects on breastfed newborns/infants are anticipated with drospirenone 4 mg.

## Keywords

breastfeeding, drospirenone 4 mg, milk concentration, plasma concentration

Date received: 1 June 2020; revised: 13 July 2020; accepted: 11 August 2020

## Introduction

Drospirenone (DRSP), a derivative of 17α-spirolactone, has a chemical structure like the aldosterone antagonist spironolactone. It has a low to moderate binding capacity to the progesterone receptor (PR), high binding properties to the mineralocorticoid receptor and a low binding affinity to the androgen receptor.[1] Drospirenone has, in relation, only 10% of the progestogenic activity of levonorgestrel on the human

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endometrium. Due to the strong anti-mineralocorticoid effect of drospirenone, the use of 2 mg in fertile women during the follicular phase caused an increase in sodium excretion. By the same way, a rise in the plasma renin activity by 100% was observed, so that the effect of sodium excretion was compensated. The aldosterone serum levels raised by 65%.[2] DRSP has also an anti-androgenic activity, approximately 30% of that of cyproterone acetate. Like dienogest, it has no estrogenic and no significant glucocorticoid activity.[3]

Also, like dienogest, DRSP has no binding affinity to the Sex Hormone–Binding Globulin (SHBG) and Corticosteroid-Binding Globulin (CBG) as in the serum. It is bound to albumin so that the free blood amount is about 3%–5%. The oral bioavailability is in a range between 75% and 85%.

Breastfeeding and the use of contraceptives are still a matter of debate. Evidence suggests that progesterone-only methods of contraception have no adverse effect on breastfeeding performance when used during lactation. Several studies demonstrated no effects of progestin-only pills (POPs) on infant growth, health or development from 6 months to 6 years of age.[4,5] Only one study has evaluated the transfer of drospirenone to breast milk after a single-dose administration of a combined pill containing 0.03 mg ethinylestradiol (EE) and 3 mg drospirenone (Yasmin, Bayer). The authors could find that the amount of DRSP measured to be transferred into breast milk in the six women participating in this study was, on average, 635 ng (range 256.2–1357.9 ng) within 24 h, corresponding to about 0.02% of the maternal dose. Based on the average concentration of the drug in breast milk over 24 h and assuming a daily ingestion of approximately 800 mL breast milk, the daily dose that reaches an infant via breast milk is estimated to be approximately 3 µg DRSP.[6]

The aim of this study hence was to assess the transfer of drospirenone to breast milk after daily administration over 7 days of the new estrogen-free contraceptive pill containing 4 mg of drospirenone (Slinda Exeltis) at steady state to evaluate the safety of this new contraceptive in breastfeeding women.

## Materials and methods

This was an open label, non-comparative single-center study. The investigational medicinal product used in this trial was the first postpartum contraceptive for study participants who were no longer breastfeeding yet were still lactating. It was administered for 7 days to achieve steady-state concentration. All participants were volunteers who planned to use oral contraceptives as their family planning method in the future. After completion of the study, all participants were supplied with a similar medication (Cerazette®, an already marketed Progesterone-Only Pill). The Ethics Committee for Clinical Research at Pauls Stradins Clinical University Hospital Development Society in Riga, Latvia, approved the trial on 19 March 2014 with the number CF111/107. The clinical study register is EudraCT no. 2013-002374-43.

**Table 1.** Patient disposition.

| Patient disposition | N | % |
|---|---|---|
| Screened | 12 | 100% |
| Violation of any inclusion/exclusion criteria | 0 | 0% |
| Voluntary discontinuation (refused treatment) | 0 | 0% |
| Intent-to-treat population (ITT population) | 12 | 100% |
| Per-protocol population (PP population) | 12 | 100% |
| Safety set (SS) | 12 | 100% |

### *Study population*

At the beginning of the study, 12 subjects were screened. Intent-to-treat, per-protocol and safety population include all 12 subjects. All subjects attended all visits and were included in the safety set to safety assessment (see Table 1).

### *Study medication, duration and blood and breast milk sampling*

The aim is to reach the steady state with the oral admisnistartion of 4 mg drsopirenone (Slinda Exeltis) during standard breakfest after the first 7 days of use. During this period, safety control procedures were performed, and breast milk was pumped twice a day to maintain lactation. At 8–12 days from the first intake of investigational drug, blood and breast milk samples were obtained simultaneously prior to 0, 1, 2, 4, 8, 12, 24, 30, 36, 48, 72 and 120 h after the last tablet administration.

The probands and newborns stayed overnight in the hospital on day 8. Serum samples were prepared and stored at −20°C until required for analysis. Milk samples were collected by pumping from both breasts empty at each of the sampling times. The milk samples were pooled from both breasts, and then split into two aliquots and frozen immediately at −20°C until required analysis.

### *Primary pharmacokinetic endpoint*

The primary objective of this trial was to assess the transfer of drospirenone to breast milk after daily administration of an oral test preparation containing 4 mg of drospirenone at the steady state.

### *Secondary pharmacokinetic endpoints*

The secondary objective of the trial was to assess the safety of the preparation based on safety clinical and laboratory measurements (at the beginning and at the end of the trial) and reporting of adverse events and/or adverse drug reactions.

### Pharmacokinetic endpoints

Descriptive evaluation for all pharmacokinetic (PK) endpoints after single repeated dose was carried out: parametric method (analysis of variance (ANOVA)-log) for the primary endpoints $C_{max}$ and area under the curve (AUC) of drospirenone after repeated dose, and 90% confidence interval (CI) for the ratio for the primary endpoints $C_{max}$ and AUC after the single repeated dose of drospirenone. Following descriptive evaluations for all pharmacokinetic (PK) endpüoints after single repeated dose were carried out:

The sample size was 12 probands. The duration of the study for each individual subject was 15 days. The blood sampling was done at 0, 1, 2, 4, 8, 12, 24, 30, 36, 48, 72 and 120 h after the administration of last pill. The milk sampling was done at 0, 1, 2, 4, 8, 12, 24, 30, 36, 48, 72 and 120 h after the administration of last pill.

### Analytical method

Analysis of drospirenone in plasma and breast samples was performed using the analytical method SOP ANE 5199.06 entitled "Determination of Drospirenone in Human EDTA Plasma over a Concentration Range of 0.25 to 100 ng/mL using a LC/MS/MS Method." PK parameters AUC (0–24 h), AUC (0–120 h) and $C_{max}$ were evaluated as PK endpoints after a single repeated dose administration of 4 mg of drospirenone in plasma and milk.

### Safety evaluation

Descriptive statistical methods were used for the evaluations of adverse events, vital signs and physical examination and clinical laboratory parameters.

## Results

### Subject disposition

For PK evaluation, all subjects who were included to the trial and received the study drug were included. None of the subjects were excluded, and all 12 were included to the PK evaluations.

All the subjects were Caucasian, the average age was 29.25 years and in median 29 years. Upper range of age was 35 years and lower 25 years. Average (on visit 1) weight was 59.5 kg, systolic blood pressure (BP) 107.8 mm Hg, diastolic BP 68.3 mm Hg, breathing rate 13.4 per minute and heart rate 72 per minute. Mean height, weight, body mass index (BMI), blood pressure, pulse and breathing rate on visit 1 are shown in Table 2.

### PKs of drospirenone in plasma

*PKs.* The PK endpoints of drospirenone were obtained from data of all 12 volunteers. The individual data obtained from plasma and milk of each volunteer are listed in Tables 3 and 4.

**Table 2.** Clinical data of the 12 subjects.

| Variable | Average | Median | Range |
|---|---|---|---|
| Age (years) | 29.25 | 29 | 25–35 |
| Weight (kg) | 59.5 | 56.9 | 52.0–74.5 |
| Systolic BP (mm Hg) | 107.8 | 110 | 90–131 |
| Diastolic BP (mm Hg) | 68.3 | 70 | 50–86 |
| Pulse rate (per minute) | 72 | 72 | 64–93 |
| Breathing rate (per minute) | 13.4 | 14 | 10–16 |

BP: blood pressure.

**Table 3.** Individual drospirenone concentrations in plasma.

| Individual | Planned draw times (h) and drospirenone concentrations in plasma (ng/mL) | | | | | |
|---|---|---|---|---|---|---|
| | Pre-dose | 1 | 2 | 4 | 8 | 12 |
| | 01 | 02 | 03 | 04 | 05 | 06 |
| 01 | 19.14 | 29.56 | 44.89 | 45.87 | 35.49 | 27.84 |
| 02 | 16.4 | 19.55 | 31.52 | 33.05 | 24.52 | 19.8 |
| 03 | 24.95 | 30.14 | 54.81 | 45.55 | 32.11 | 29.32 |
| 04 | 13.2 | 14.22 | 23.84 | 43.33 | 28.72 | 23.11 |
| 05 | 27.25 | 25.39 | 44.77 | 51.42 | 34.75 | 31.19 |
| 06 | 7.92 | 20.46 | 28.69 | 30.44 | 17.02 | 14.41 |
| 07 | 13.26 | 34.61 | 44.5 | 46.29 | 22.68 | 18.83 |
| 08 | 20.05 | 25.45 | 68.45 | 52.88 | 32.39 | 26.49 |
| 09 | 14.83 | 41.4 | 57.81 | 49.34 | 27.23 | 24.66 |
| 10 | 14.29 | 42.09 | 47.7 | 42.01 | 26.36 | 21.36 |
| 11 | 17.33 | 26.1 | 47.72 | 37.57 | 27.79 | 24.48 |
| 12 | 26.23 | 56.77 | 51.35 | 37.37 | 27.3 | 20.59 |
| Individual | Planned draw times (h) and drospirenone concentrations in plasma (ng/mL) | | | | | |
| | 24 | 30 | 36 | 48 | 72 | 120 |
| | 07 | 08 | 09 | 10 | 11 | 12 |
| 01 | 18.32 | 15.79 | 11.22 | 7.3 | 3.62 | 0.28 |
| 02 | 16.08 | 12.78 | 10.64 | 6.68 | 2.61 | 0.44 |
| 03 | 28.29 | 27.5 | 23.67 | 20.88 | 13.52 | 6.92 |
| 04 | 11.89 | 9.16 | 6.46 | 4.52 | 9.91 | <0.25 |
| 05 | 25.15 | 20.41 | 18.54 | 13.49 | <0.25 | 1.43 |
| 06 | 8.27 | 4.87 | 4.06 | 2.94 | 1.21 | <0.25 |
| 07 | 11.78 | 10.73 | 8.67 | 6.94 | 3.29 | 0.79 |
| 08 | 19.71 | 15.12 | 13.75 | 9.03 | 4.48 | 0.97 |
| 09 | 15.5 | 11.64 | 10.93 | 6.45 | 2.74 | 0.49 |
| 10 | 13.04 | 9.65 | 8.21 | 4.84 | 1.67 | <0.25 |
| 11 | 16.69 | 12.15 | 11.43 | 7.85 | 3.89 | 0.92 |
| 12 | 12.66 | 8.91 | 8.24 | 4.17 | 1.67 | 0.30 |

<0.25 indicates the lowest reference measurement value.

The average concentration–time curve of drospirenone in plasma 24 h after the administration of the last dose (AUC (0–24 h)) was 635.33 ng h/mL and 120 h after the single repeat dose administration (AUC (0–120 h)) was 1180.57 ng h/mL, respectively. The average $C_{max}$ was 48.64 ng/mL.

**Table 4.** Individual drospirenone concentrations in milk.

| Individual | Planned draw times (h) and drospirenone concentrations in milk (ng/mL) | | | | | |
|---|---|---|---|---|---|---|
| | Pre-dose | 1 | 2 | 4 | 8 | 12 |
| | 01 | 02 | 03 | 04 | 05 | 06 |
| 01 | 3.14 | 4.60 | 5.52 | 2.34 | 4.21 | 3.97 |
| 02 | K (*) | 3.08 | 2.24 | 2.07 | 1.45 | 1.98 |
| 03 | 7.86 | 9.58 | 13.61 | 37.16 | 22.89 | 23.48 |
| 04 | 3.29 | 4.19 | 11.01 | 6.35 | 4.25 | 3.89 |
| 05 | 6.15 | 3.85 | 6.50 | 7.78 | 5.56 | 4.74 |
| 06 | 1.72 | 2.58 | 6.32 | 6.46 | 4.11 | 3.05 |
| 07 | 1.44 | 3.68 | 4.67 | 5.20 | 4.02 | 3.20 |
| 08 | 1.72 | 2.05 | 5.32 | 6.25 | 4.58 | 4.06 |
| 09 | 2.90 | 6.30 | 10.35 | 9.60 | 7.09 | 4.84 |
| 10 | 3.51 | 7.62 | 14.60 | 12.59 | 8.46 | 6.25 |
| 11 | 3.55 | 4.35 | 4.78 | 10.16 | 6.45 | 5.84 |
| 12 | 2.71 | 4.97 | 5.42 | 6.52 | 5.79 | 3.85 |
| Individual | Planned draw times (h) and drospirenone concentrations in milk (ng/mL) | | | | | |
| | 24 | 30 | 36 | 48 | 72 | 120 |
| | 07 | 08 | 09 | 10 | 11 | 12 |
| 01 | 1.40 | 2.34 | 1.02 | 2.10 | 0.57 | <0.25 |
| 02 | 1.61 | 1.76 | 2.03 | 1.04 | 0.68 | 0.47 |
| 03 | 6.06 | 9.17 | 3.01 | 0.94 | 1.75 | 0.73 |
| 04 | 1.90 | 4.61 | 1.38 | 0.69 | 0.30 | <0.25 |
| 05 | 3.05 | 2.57 | 1.87 | 1.83 | 1.49 | 0.27 |
| 06 | 2.15 | 1.50 | 1.55 | 0.80 | 0.38 | <0.25 |
| 07 | 1.23 | 1.06 | 1.06 | 0.90 | 0.43 | 0.27 |
| 08 | 2.77 | 2.68 | 2.07 | 1.32 | 0.65 | <0.25 |
| 09 | 3.49 | 3.21 | 2.25 | 1.22 | 0.56 | <0.25 |
| 10 | 3.06 | 2.10 | 1.70 | 1.00 | 0.37 | <0.25 |
| 11 | 3.24 | 2.44 | 2.12 | 1.21 | 0.71 | 0.29 |
| 12 | 2.22 | 1.76 | 1.60 | 0.69 | 0.28 | <0.25 |

*Value is missing.
<0.25 indicates the lowest reference measurement value.

The average concentration–time curve of drospirenone in milk 24 h after the administration of the last dose (AUC (0–24 h)) was 134.35 ng h/mL and 120 h after the single repeat dose administration (AUC (0–120 h)) was 227.17 ng h/mL, respectively. The average $C_{max}$ was 10.34 ng/mL.

From these data, we can conclude that on average, 18.13% of plasma drospirenone made it to breast milk and that the highest concentration of drospirenone in breast milk was 17.55% of that in plasma. The total quantity of drospirenone passing to breast milk is on average 4478 ng during a 24-h period representing 0.11% of the maternal daily dose.

A summary of the descriptive statistics of all PK endpoints of drospirenone is presented in Table 5 and Figures 1 and 2 for plasma and milk, respectively. The milk to plasma ratio of PK parameters is presented in Table 6.

### *Pharmacokinetics of drospirenone in breast milk*

The average drospirenone concentration in breast milk over the 24-h period ranged from 1.90 to 19.22 ng/mL, with an average value of 5.60 ± 4.51 ng/mL assuming that an average daily intake of breast milk by an infant is 800 mL,[7] the total quantity of drospirenone passing to breast milk is 4478 ng during 24 h after the last dose of single repeat daily administration of drospirenone.

The average drospirenone concentration in breast milk over the 120-h period ranged from 1.12 to 5.49 ng/mL, with an average value of 1.89 ± 1.19 ng/mL. Hence, the total quantity of drospirenone passing to breast milk is 7572 ng during 120 h after the last dose of single repeated daily administration of drospirenone.

### *Adverse events*

No serious adverse events were reported in the course of the trial. No clinically relevant laboratory changes or trends were observed during the study. The laboratory and clinical screening revealed no indications for adverse events or poor tolerability.

## Discussion

After a single administration of 3 mg drospirenone in combined oral contraceptives, serum levels of 35 ng/mL can be measured after 1–2 h of intake. After this peak, the levels go down, but 24 h later, the DRSP concentrations in the serum remain at values of 20–25 ng/mL. This is the reason why an accumulation of drospirenone in blood after repeated dosing, and treatment in combination with estrogens leads to peak serum concentrations of 60 ng/mL after 7–10 days. Drospirenone is depleted through a metabolic pathway that consists in the opening of the lactone ring resulting in an acid group. Afterward, a reduction of the Δ4-double bond is performed;[8] DRSP half-lives are 1.6 h (t1/2α) and 27 h (t1/2β).

Recent studies on a new 4 mg non-micronized drospirenone-only pill (Slinda Exeltis) found that after repeated dose administration, the mean ratio of drospirenone alone versus the combination to a 0.02 mg EE and 3 mg drospirenone (Yaz, Bayer) formulation was only 76.5% and after applying a dose correction 58.4%. The accumulation ratio $R_{ac}$ (AUC) was 1.9 for the product containing drospirenone alone, while it was 2.8 for drospirenone in combination with EE. These findings indicate that, after repeated dosing, there is an influence of EE on the PK of drospirenone. The total exposure to drospirenone is statistically significantly lower for drospirenone alone, even though the individual strength in the tablet formulations is higher (4 mg vs 3 mg).[9]

This study investigated the transfer of drospirenone to breast milk following a repeated oral administration of the

**Table 5.** Pharmacokinetic endpoints in plasma and milk of drospirenone after 7 × 4 mg of DRSP.

| Plasma | | | | | | | |
|---|---|---|---|---|---|---|---|
| Variable | Geometric mean | Arithmetic mean | SD | CV | Range | Median | N |
| $C_{max}$ (ng/mL) | 47.54 | 48.64 | 10.47 | 21.5 | 30.44–68.45 | 47.71 | 12 |
| $t_{max}$ (h) | 2.67 | 2.92 | 1.16 | 39.9 | 1–4 | 3 | 12 |
| AUC (0–24 h) (ng h/mL) | 623.93 | 635.33 | 121.00 | 19.0 | 391.76–799.85 | 615.55 | 12 |
| AUC (0–120 h) (ng h/mL) | 1122.83 | 1180.57 | 416.67 | 35.3 | 581.81–2285.76 | 1135.76 | 12 |
| Milk | | | | | | | |
| Variable | Geometric mean | Arithmetic mean | SD | CV | Range | Median | N |
| $C_{max}$ (ng/mL) | 8.34 | 10.34 | 9.01 | 87.14 | 3.08–37.16 | 7.15 | 12 |
| $t_{max}$ (h) | 2.83 | 3.08 | 1.16 | 37.8 | 1–4 | 4 | 12 |
| AUC (0–24 h) (ng h/mL) | 112.57 | 134.35 | 108.20 | 80.5 | 45.68–461.17 | 101.11 | 12 |
| AUC (0–120 h) (ng h/mL) | 203.61 | 227.17 | 142.69 | 62.8 | 133.82–658.90 | 181.58 | 12 |

SD: standard deviation; CV: coefficient of variation; AUC: area under the curve.

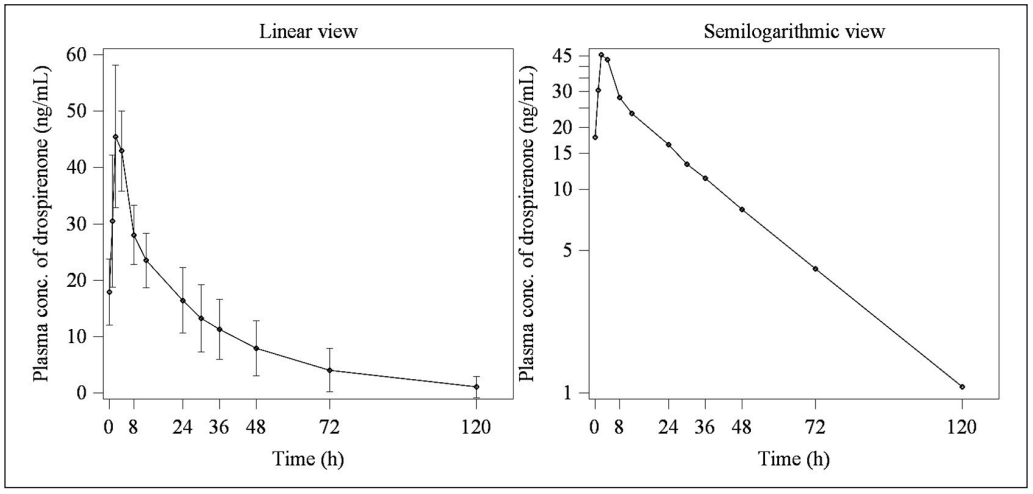


**Figure 1.** Arithmetic mean (±SD) plasma concentrations of drospirenone versus time curve (linear and semilogarithmic).

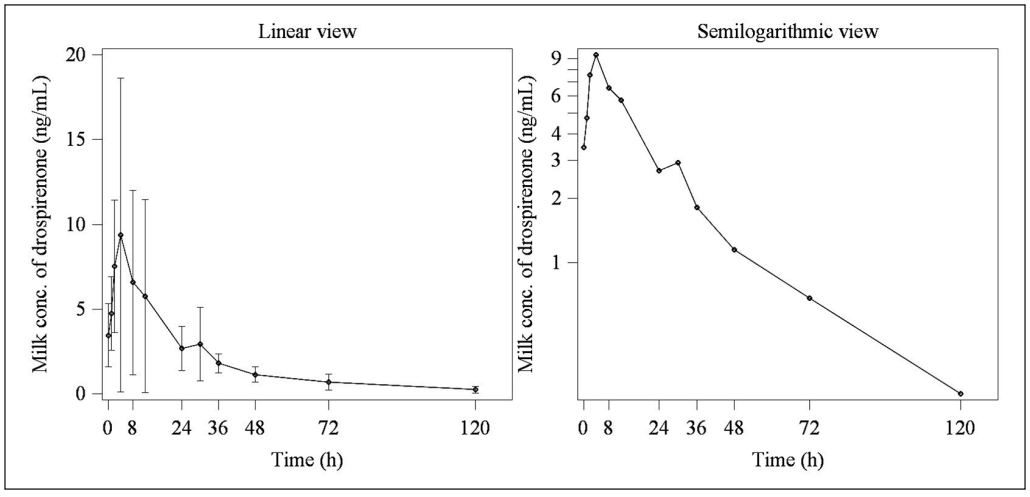


**Figure 2.** Arithmetic mean (±SD) milk concentrations of drospirenone versus time curve (linear and semilogarithmic).

**Table 6.** Milk to plasma ratios.

| Variable | Method | Point estimator | Confidence interval | CV (%) |
|---|---|---|---|---|
| $C_{max}$ (ratio milk/plasma) | ANOVA-log | 17.55% | 12.61%–24.41% | 49.83% |
| AUC (0–24 h) (ratio milk/plasma) | ANOVA-log | 18.04% | 13.42%–24.26% | 44.17% |
| AUC (0–120 h) (ratio milk/plasma) | ANOVA-log | 18.13% | 13.85%–23.75% | 39.95% |

CV: coefficient of variation; ANOVA: analysis of variance; AUC: area under the curve.

new estrogen-free contraceptive containing 4 mg drospirenone. The PK parameters of drospirenone in serum and in breast milk were in a similar range to previous single oral dose studies of 3 mg DRSP + 30 µg EE and indicate that lactation does not influence the PKs of the drug.[10]

The transfer of steroid hormones used in other contraceptives into breast milk has been reported previously. Milk to plasma or serum concentration ratios of about 0.1–0.34 have been reported for norethisterone and for levonorgestrel after single or repeated oral administration of different doses of the drug, either alone or in combination with EE.[7,11,12] The corresponding ratios following oral administration of cyproterone acetate[13] and megestrol acetate[14] were reported to be about 0.36 and 0.8, respectively; however, with a large interindividual variation observed in all studies, which was not seen in this study. A similar variability emerged when the milk to plasma or serum ratios were calculated based on AUC data. Thus, the fraction of DRSP transferred to breast milk observed in this study is consistent with the range reported for other progestogens used in oral contraceptives. For EE, a milk to plasma ratio of 0.25 has been reported.[15]

The amount of drospirenone transferred to the infant by breast milk has been calculated based on the average concentration of DRSP found in breast milk 24 h after tablet administration and the average milk volume known to be ingested by a 2–5-month-old infant. The value of drospirenone passing to the breast milk was in this study 4478 ng during a period of 24 h representing 0.11% of the maternal daily dose. This amount is negligible and so it has been stated in the summary of product characteristics of the product in the United States and Europe.[16,17]

This estrogen-free contraceptive containing 4 mg of drospirenone in a 24/4 regimen intake provides effective contraception with a good safety/tolerability profile in a broad group of women, including breast feeding women and is an option for most women with cardiovascular risk factors like high BMI or thromboembolic risks also in the time after delivery.

## Conclusion

If an average daily infant intake of breast milk is 800 mL, 24 h after the oral administration of 4 mg of drospirenone, the total quantity of daily drospirenone intake by the mother passing into breast milk is 4478 ng. If an average daily infant intake of breast milk is 800 mL, 120 h after the oral administration of 4 mg of drospirenone, the total quantity of daily drospirenone intake by the mother passing to breast milk is 7572 ng. The highest concentration of drospirenone in breast milk was 17.55% of that in plasma. The total quantity of drospirenone passing to breast milk is on average 4478 ng during a 24-h period representing 0.11% of the maternal daily dose. Thus, at therapeutic doses of the product, no effects on the breastfed newborns/infants are anticipated.

### Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: P.-A.R. and E.C. are the employees of Exeltis HealthCare. D.M. and K.K. declare no conflict of interest.

### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: This study was funded by the Insud Pharma, Spain.

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