Correction to: Clinical Pharmacokinetic Characteristics of Cebranopadol, a Novel First-in-Class Analgesic

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Correction to: Clin Pharmacokinet (2018) 57:31–50
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Page 40, column 2, para 1 which reads as
For each simulation, PK profiles from 1000 subjects were simulated based on a titration scheme of 100 μg for 6 days, 200 μg for 6 days and 400 μg for 6 days to reach the cebranopadol target dose of 600 μg. Median values of maximum concentration at steady state (C_{max,ss}) and area under the curve at steady state (AUC_{ss}) were calculated. The time to reach steady state was calculated as the time point when the AUC reaches 98% of the AUC at absolute steady state, e.g. maximum AUC value during a duration of 50 days.

should read
For each deterministic simulation (i.e., the interindividual variability was fixed to 0), one subject PK profile was simulated based on an optimized titration scheme to reach the cebranopadol target dose of 600 μg (100 μg of 6 days, 200 μg of 6 days, 400 μg of 6 days and 600 μg). The steady-state was defined to be achieved on Day 40 in the simulation to calculate the values of maximum concentration at steady state (C_{max,ss}) and area under the curve at steady state (AUC_{ss}) as reported in Table 14.

Page 45, column 2, para 4 which reads as
As shown in Table 14, the impact of age and body weight on C_{max,ss} and AUC_{ss} was lower than 3% with respect to the values of the typical patient considered as reference, whereas the impact of lower CrCl values accounted for increases in C_{max,ss} and AUC_{ss} up to 30 and 34% in the investigated range, respectively. Females had 13% higher C_{max,ss} and 17% higher AUC_{ss} than males due to the fact that sex significantly correlated with clearance (Table 14). As the histogram in Fig. 4 shows, a considerable overlap exists between the distributions of male and female clearances.

should read
As shown in Table 14, the impact of age and body weight on C_{max,ss} and AUC_{ss} was lower or equal to 1% with respect to the values of the typical patient considered as reference, whereas the impact of lower CrCl values accounted for increases in C_{max,ss} and AUC_{ss} up to 28 and 34% in the investigated range, respectively. Females had 14% higher C_{max,ss} and 17% higher AUC_{ss} than males due to the fact that sex significantly correlated with clearance (Table 14). As the histogram in Fig. 4 shows, a considerable overlap exists between the distributions of male and female clearances.

Page 45, column 2, para 5 and page 46, column 1, para 1 which read as
The simulations also indicated that low back pain/os-teoarthritis and diabetic polyneuropathy patient populations can have up to 29.5% higher C_{max,ss} and AUC_{ss} values compared with healthy subjects (Table 14).
The simulations also indicated that low back pain/os- 
teoarthritis, bunionectomy and diabetic polyneuropathy 
patient populations can have 19–114% higher $C_{\text{max,ss}}$ and 
$\text{AUC}_{\text{ss}}$ values compared with healthy subjects (Table 14).

Page 46, Table 13, column 1, rows 27 and 28 which read 
Bunionectomy patients
DPN patients
should read
DPN patients
Bunionectomy patients

Page 48, Table 14 should appear as

| Covariate          | $C_{\text{max,ss}}$ (pg/mL) | $\%$ Change in $C_{\text{max,ss}}$ | $\text{AUC}_{\text{ss}}$ (pg h/mL) | $\%$ Change in $\text{AUC}_{\text{ss}}$ |
|--------------------|-----------------------------|-----------------------------------|-----------------------------------|-------------------------------------|
| Reference values   | 378                         | 0                                 | 6790                              | 0                                   |
| Female sex         | 432                         | 14                                | 7960                              | 17                                  |
| Age (years)        |                             |                                   |                                   |                                     |
| 40                 | 375                         | - 1                               | 6790                              | 0                                   |
| 60                 | 379                         | 0                                 | 6790                              | 0                                   |
| 75                 | 381                         | 1                                 | 6790                              | 0                                   |
| CrCl (mL/min)      |                             |                                   |                                   |                                     |
| 45                 | 483                         | 28                                | 9080                              | 34                                  |
| 60                 | 446                         | 18                                | 8250                              | 21                                  |
| 80                 | 410                         | 9                                 | 7480                              | 10                                  |
| Body weight (kg)   |                             |                                   |                                   |                                     |
| 70                 | 379                         | 0                                 | 6810                              | 0                                   |
| 100                | 377                         | 0                                 | 6760                              | - 1                                 |
| 120                | 375                         | - 1                               | 6720                              | - 1                                 |
| Disease status     |                             |                                   |                                   |                                     |
| Healthy            | 316                         | - 16                              | 5690                              | - 16                                |
| DPN                | 428                         | 13                                | 7690                              | 13                                  |
| Bunionectomy patients | 681                | 80                                | 12200                             | 80                                  |

The titration scheme to reach cebranopadol 600 µg is defined as 
cebranopadol 100 µg for 6 days, cebranopadol 200 µg for 6 days, 
cebranopadol 400 µg for 6 days and cebranopadol 600 µg

The reference values for the covariates, defined as the median values 
for continuous covariates and the most frequent category for cate-
gorical covariates, except disease status, were: sex = male, formula-
tion = tablet, CYP2C9 status = unknown, disease status = LBP and 
OA patients, age (years) = 55, CrCl (mL/min) = 106.4, body weight 
(kg) = 82, ALT (units/L) = 19

ALT alanine transferase, $\text{AUC}_{\text{ss}}$ area under the plasma concentration-
time curve for one 24 h dosing interval at steady state, $C_{\text{max,ss}}$ max-
imum plasma concentration at steady state, $\text{CrCl}$ creatinine clearance, 
CYP cytochrome P450, DPN diabetic polyneuropathy, LBP low back 
pain, OA osteoarthritis

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indicate if changes were made.