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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi Drug substance(s): PrLasix® Special (furosemide)	Study Identifiers: NCT01724788, U1111-1127-0839 Study code: FUROSL06121
Title of the study: Pharmacokinetic profile and pharmacodynamic characteristics of a furosemide high-dosage formulation (PrLasix® Special, tablets 500 mg) in patients with chronic renal failure undergoing peritoneal dialysis.	
Study center(s): One Canadian centre.	
Study period: Date first patient enrolled: 05/Nov/2012 Date last patient completed: 29/Jan/2013	
Phase of development: Phase 1	
Objectives: Primary: To determine the absolute bioavailability of the furosemide 500 mg (PrLasix® Special) oral formulation in patients with chronic renal failure undergoing peritoneal dialysis. Secondary: • To determine the pharmacokinetic (PK) profiles of furosemide 500 mg (PrLasix® Special) oral formulation and 250 mg intravenous (IV) formulation. • To compare the pharmacodynamic (PD) characteristics of furosemide 500 mg (PrLasix® Special) oral formulation with 250 mg IV furosemide.	
Methodology: Monocentre, open-label, randomized, two-treatment, two-period, cross-over, prospective study.	
Number of patients: Planned: 12 Randomized: 12 Treated: 12 Evaluated: Pharmacodynamics: 12 Safety: 12 Pharmacokinetics: 12	
Diagnosis and criteria for inclusion: • Male or female, 18 years old or older, with chronic renal failure who underwent peritoneal dialysis for at least 3 months. • Able to communicate well with the investigator and able to comply with the requirements of the entire study. • Women of childbearing age were required to have a negative pregnancy test before administration of the study drug. • Written informed consent was obtained.	

Study treatments

Investigational medicinal product(s): Furosemide 500 mg (^{Pr}Lasix® Special 500 mg)

Formulation: Tablet

Route(s) of administration: Oral, in fasted conditions

Dose regimen: 500 mg single dose

Comparator: Furosemide special injection

Formulation: Injection 250 mg/25 mL

Route(s) of administration: IV

Dose regimen: 250 mg, IV infusion in 250 mL normal saline (via catheter, over 60 minutes), single dose

Duration of treatment: Furosemide 500 mg tablet: 1 day; furosemide special 250 mg injection: 1 day

Duration of observation: 14 days

Criteria for evaluation:

Pharmacodynamics: The PD characteristics of oral and IV furosemide were measured at specific times(T = 0, 6, 12, 24 hours)

The measurements included the urinary volume, excretion of water, sodium, potassium, chloride, calcium, magnesium, urea, and creatinine at times 0, 6, 12 and 24 hours.

Safety: Safety was evaluated through the assessment of treatment-emergent adverse events, laboratory tests, and vital signs.

Pharmacokinetics:

Primary: The absolute bioavailability (F) of a single 500 mg oral tablet in patients with chronic renal failure undergoing peritoneal dialysis was measured by the dose-corrected area under curve (AUC_∞) oral tablet divided by AUC_∞ IV:

$F = AUC_{PO\infty} \times DIV / AUCIV_\infty \times D_{PO}$.

F = absolute bioavailability of the orally administered dose (D) (%).

Secondary:

The PK profile of furosemide (oral and IV) was measured by the following parameters:

C_{max} = maximum (peak) plasma drug concentration after single dose administration.

T_{max} = time to reach peak or maximum concentration following drug administration.

$T_{½}$ = elimination half-life (hours).

k_e or λ_z = elimination rate constant (the rate at which furosemide is removed from the body).

AUC_{T0-72} = area under curve from the time zero to 72 hours.

AUC_∞ = area under curve from the time zero to infinity (µg/mL x h). The AUC_∞ is estimated by the linear trapezoidal rule from time zero to the last measurable concentration (C) and extrapolated to infinity by the equation C/λ_z.

$AUMC_\infty$ = total area under the first moment curve of plasma drug concentration vs. time.

MRT= mean residence time (hours) = $AUMC_\infty/AUC_\infty$

For IV only:

Vd = apparent volume of distribution (quantify the distribution of furosemide between plasma and the rest of the body after oral and IV dosing respectively.

CL = total body (systemic) clearance of drug from plasma (serum) (ml/min) = D / AUC_∞

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Furosemide oral: 0 minute, 20 minutes, 40 minutes, 1 hour, 1 hour 20 minutes, 1 hour 40 minutes, 2 hours, 4 hours, 6 hours, 9 hours,12 hours, 24 hours, 48 hours, and 72 hours after administration.

Furosemide IV: 0 minute, 10 minutes, 20 minutes, 30 minutes, 40 minutes, 50 minutes, 1 hour, 1 hour 15 minutes, 1 hour 30 minutes, 2 hours, 4 hours, 6 hours, 9 hours,12 hours, 24 hours, 48 hours, and 72 hours after administration.

The plasma concentration of furosemide was determined by using a liquid chromatography with tandem mass spectrometry (LC/MS/MS) assay. The lower limit of quantification (LLOQ) was 0.3 µg/mL using a sample volume of 0.2 mL.

Statistical methods: The primary objective of the study was to determine the absolute bioavailability of furosemide following a single oral dose of 500 mg. With 12 subjects, the maximum imprecision for each PK parameter was ± 0.566 x standard deviation (SD), where the imprecision was based on a 95% confidence interval (CI). A non-compartmental approach with a log-linear terminal phase assumption was used to estimate the main absorption and disposition parameters. The AUC was estimated using trapezoidal rule, and the terminal phase was estimated by maximizing the coefficient of determination estimated from the log-linear regression model. Descriptive statistics were calculated for furosemide plasma concentration at each individual data point and for all PK parameters. The PK parameters C_{max}, λ_z, $T_{1/2}$, $AUC_{T0\text{-}72h}$, AUC_{∞}, $AUMC_{\infty}$, MRT, Vd, and CL were log-transformed. These parameters (untransformed and transformed) were analysed using an analysis of variance mixed effects model:
Parameter = Sequence (Patients) + Period + Treatment (Oral versus IV) + Error, with the parameter as independent variable, with the sequence, period and treatment as fixed effect, and the patients nested in sequence as a random effect. The geometric mean and 90% CIs were estimated for each treatment. The parameter T_{max} was analysed using a non-parametric approach. The fixed effect of sequence, period, and treatment on T_{max} was tested based on the non-asymptotical Wilcoxon's rank sum test (Mann-Whitney U-test).

The PD variables urine volume and weight were analysed using mean, SD, median, and interquartile and complete ranges. Cumulative urine volume and weight at 6 hours, 12 hours, and 24 hours were analysed adjusting for urine volume and weight at T0 (-12 hours to T0). Inferential statistics were obtained using the analysis of variance mixed effects mode as was used for the PK parameters.

The safety variables were analysed descriptively.

Summary:

Population characteristics: All 12 patients (8 males, 4 females) who were screened were randomised and included in the evaluation of PK, PD, and safety parameters. All patients completed the study according to the protocol. The majority (58.3%) of patients were white. Median (range) value for age was 48 (33-76) years, for body weight was 71.8 (52.5 to 102.0) kg, for body mass index (BMI) was 24.8 kg/m^2 (20.3 to 39.9 kg/m^2), and for height was 170 (150 to 178) cm. There were no relevant differences between the treatment groups with respect to demographics or disease characteristics.

Pharmacodynamic results: At 24 hours post administration, urine volume and urine weight were slightly higher in patients who received furosemide 500 mg orally than in patients receiving 250 mg IV. Urine weights and cumulative urine volumes at 24 hours after furosemide administration were within the norm. No statistically significant differences were found between furosemide 500 mg oral and furosemide 250 mg IV in cumulative urine volume or urine weight at any of the time points measured. Urine electrolyte concentrations were within normal ranges at the different time points measured. At 24 hours post dosing, statistically significant differences were found for the change in urine sodium and calcium between furosemide 500 mg oral and furosemide 250 mg IV treatment. Furthermore, the change in chloride and the change in lowest urine calcium concentration at 6 hours after administration were also statistically significantly different between the two treatments. Both urea and creatinine concentrations in urine decreased after administration of furosemide 500 mg oral or furosemide 250 mg IV. The levels were within normal ranges, and there were no statistically significant differences between the two treatments with regard to the changes in urea and creatinine levels in urine at any of the time points measured.

Safety results: In total, 4 patients reported treatment-emergent adverse events (TEAEs) during the study: one (8.3%) of the patients experienced 1 TEAE after receiving furosemide 500 mg orally and 3 (25.0%) of the patients experienced 6 TEAEs after receiving furosemide 250 mg IV. All the TEAEs were of mild or moderate intensity and none of the TEAEs were assessed as related to the study medication. Only single occurrences of TEAEs were reported with the exception of nasopharyngitis which occurred in 2 (16.7%) of the 12 patients after furosemide 250 mg administration. There were no deaths, serious adverse events (SAEs), or TEAEs leading to withdrawal during this study. Two TEAEs occurring after furosemide 250 mg IV application required counteractive treatment. Laboratory values did not show any clinically relevant changes between the baseline and last measurement. After intake of the study medication, no clinically relevant alterations were observed for vital signs except for one event of neurogenic shock after administration of furosemide 250 mg IV.

Overall, the safety data obtained in the present study indicate that administration of furosemide 500 mg oral or furosemide 250 mg IV was safe and well tolerated.

Pharmacokinetic results: The absolute bioavailability of the 500 mg oral formulation of furosemide as determined by comparison with furosemide 250 mg IV was 51.9%. No sequence-effect was detected. Dose-corrected C_{max} indicated a lower peak concentration after the application of furosemide 500 mg oral when compared with furosemide 250 mg IV (geometric mean ratio 0.25, P = 0.0001). Dose-corrected AUC_{T0-72h} and AUC_{∞} values were lower after oral intake of furosemide 500 mg than after IV administration of furosemide 250 mg (geometric mean ratios 0.46 and 0.47 respectively, P = 0.0001). The k_e value was also lower for furosemide 500 mg oral compared to furosemide 250 mg IV (geometric mean ratio 0.69, P = 0.0173). $AUMC_{\infty}$ was higher and the elimination half-time ($t_{1/2}$) and MRT were longer for furosemide 500 mg oral compared to furosemide 250 mg IV (all P < 0.05).

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