## What is known about the pharmacokinetics of FORTEO® (teriparatide injection)?

### SUMMARY

- The pharmacokinetic profile of teriparatide was characterized in a series of conventional clinical pharmacology studies and population pharmacokinetic analyses in healthy men and women, patients with mild to severe renal insufficiency, and patients with osteoporosis.[1]
- Teriparatide is absorbed after subcutaneous injection. It reaches peak serum concentrations about 30 minutes after subcutaneous injection of a 20-µg dose and has a $T_{1/2}$ of approximately 1 hour.[2]
- Drug accumulation did not occur with daily dosing in patients treated with teriparatide for up to 2 years.[1]
- Systemic clearance exceeds the rate of normal liver plasma flow, which is consistent with both hepatic and extra-hepatic clearance.[2]
- Although systemic exposure to teriparatide was approximately 20% to 30% lower in men than women, the recommended dosage for men and women is the same.[2]
- There were no major differences in the pharmacokinetics of teriparatide in regard to race; however, due to the limited number of non-Caucasian patients, the influence of race cannot be conclusively determined.[1]
- No pharmacokinetic differences were identified in patients with creatinine clearance 30 to 72 mL/minute administered a single dose of teriparatide. In patients with severe renal impairment (creatinine clearance <30 mL/minute), the AUC and $T_{1/2}$ of teriparatide were increased.[2]
- No studies have been performed in patients with hepatic impairment.[2]
- The pharmacokinetics of teriparatide does not appear to be affected by age, body weight, heart failure, alcohol intake, or smoking status.[1]
- Following once-daily subcutaneous administration, teriparatide produces a modest but transient increase in serum calcium.[3]
- The pharmacokinetic findings for Japanese PMW with osteoporosis appeared to be similar to those for healthy Japanese PMW and were also consistent with analyses of pharmacokinetic data from the FPT.[4]
- In another study of teriparatide in Japanese PMW with osteoporosis, the plasma $C_{max}$ was achieved 1 hour after a single injection in both the 28.2-µg and 56.5-µg groups and the teriparatide concentration disappeared 6 hours after the injection. Serum-corrected calcium increased rapidly, reached its peak value 4 to 6 hours after administration, and returned to baseline 24 hours after administration.[5]

### ABSORPTION

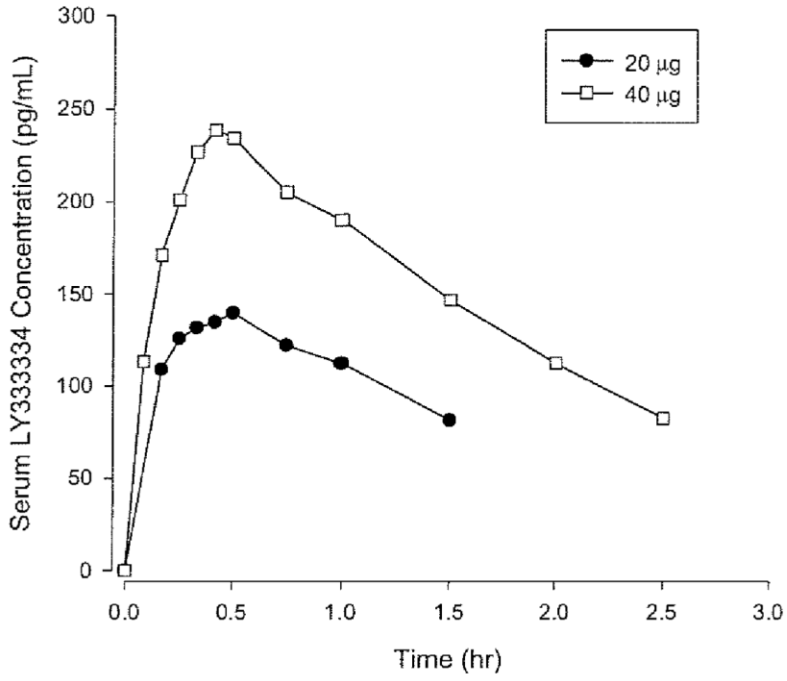
Teriparatide is rapidly and extensively absorbed from the subcutaneous tissue following subcutaneous injection into the abdominal wall or thigh.[1]

The estimated absolute bioavailability is 95% based on pooled data from 20-, 40-, and 80-µg doses. Maximum serum concentrations are achieved approximately 30 minutes following a subcutaneous injection of teriparatide 20 µg (Figure 1).[2]

Peak molar concentrations of teriparatide briefly exceed the upper limit of normal (ULN) for endogenous parathyroid hormone (PTH) by 4- to 5-fold. However, mean systemic exposure to teriparatide plus endogenous PTH over 24 hours is less than the exposure to endogenous PTH, assuming a constant concentration of PTH at the ULN (65 pg/mL [7.0 pM]).[1]

Serum concentration returns to nonquantifiable levels within 3 hours.[2]

**Figure 1. Representative Mean Serum Concentration vs Time Profiles for a Single Dose of Teriparatide[1]**




Abbreviation: LY333334 = teriparatide.

Because teriparatide has a rapid systemic clearance, accumulation of teriparatide does not occur with daily dosing, as demonstrated by similar total systemic exposure in healthy subjects receiving single doses of the drug and patients who were treated for up to 2 years.[1]

Teriparatide exhibits linear pharmacokinetics at doses of 5 µg to 100 µg.[1]

## DISTRIBUTION

Systemic clearance of teriparatide (approximately 62 L/hr in women and 94 L/hr in men) exceeds the rate of normal liver plasma flow, consistent with both hepatic and extra-hepatic clearance.[2]

Intersubject variability in systemic clearance and volume of distribution is 25% to 50%.[1]

The half life ($T_{1/2}$) of teriparatide in serum is 5 minutes when administered by intravenous injection and approximately 1 hour when administered by subcutaneous injection. The longer $T_{1/2}$ following subcutaneous administration reflects the time required for absorption from the injection site.[1]

## METABOLISM

The mechanism by which teriparatide is metabolized has not been studied. However, the metabolism and excretion of human, rat, and bovine intact PTH and synthetic PTH(1-34) have been reviewed in the published literature. According to these data, the metabolism of synthetic and/or endogenous PTH involves the liver, kidney, and to some extent, bone.[6-9]

Peripheral metabolism of PTH is believed to occur by nonspecific enzymatic mechanisms in the liver followed by excretion via the kidneys.[2]

The kidney plays a significant role in the clearance of intact PTH and its metabolites through glomerular filtration with tubular reabsorption.[6,9]

## SPECIAL POPULATIONS

Population pharmacokinetic approaches were employed in 2 phase 3 studies performed in postmenopausal women (PMW) and men with osteoporosis to measure teriparatide's disposition based on the influences of

- hepatic function
- renal function
- age
- gender
- smoking status, and
- alcohol consumption.[1]

Conventional clinical pharmacology studies were used to examine potential influences of chronic renal insufficiency and cardiac failure.[1]

### Gender

Systemic exposure to teriparatide is approximately 20% to 30% lower in men than in women.[2] However, the $T_{1/2}$ of disappearance from systemic circulation was similar in both men and women.[1]

No significant gender differences were detected in clinical trials with respect to

- safety
- tolerability, or
- lumber spine bone mineral density (BMD) response.[1]

The recommended dose for both genders is 20 µg/day.[2]

### Race

Patients evaluated in clinical investigations with teriparatide were predominantly Caucasian; less than 1.5% were Hispanic, Asian, or of other origins.[1]

No major pharmacokinetic differences were detected with respect to race. However, due to the limited number of non-Caucasian patients, the influence of race cannot be conclusively determined.[1,2]

### Renal Impairment

No pharmacokinetic differences were identified in 11 patients with creatinine clearance [CrCl] 30 to 72 mL/min administered a single dose of teriparatide.[2]

In 5 patients with severe renal impairment (CrCl <30 mL/min), the area under the curve (AUC) and $T_{1/2}$ of teriparatide were increased by 73% and 77%, respectively.[2]

Maximum serum concentration of teriparatide was not increased. No studies have been performed in patients undergoing dialysis for chronic renal failure.[2]

### Hepatic Failure

Nonspecific proteolytic enzymes in the liver (possibly Kupffer cells) cleave PTH(1-34) and PTH(1-84) into fragments that are cleared from circulation mainly by the kidney.[2]

Since hepatic Kupffer cells are the principal site for the cleavage of PTH(1-34) into fragments, the rate of clearance by this high-capacity system would be affected only by reduced hepatic blood flow rather than by hepatic insufficiency.[1] However, no studies have been performed in patients with hepatic impairment.[2]

In population pharmacokinetic analyses of 2 clinical studies, no significant associations were found between pharmacokinetic parameters of teriparatide and concentrations of

- serum bilirubin
- alanine aminotransferase (ALT)
- aspartate aminotransferase (AST), or
- gamma-glutamyltransferase (GGT).[1]

Patients with impaired hepatic function and ascites may have an altered volume of distribution; however, the pharmacokinetics of teriparatide has not been evaluated in patients with ascites.[1]

### Age

No significant differences in teriparatide pharmacokinetic parameters were identified with respect to patient age (range 31-85 years).[2]

### Body Weight

No alterations in the clearance of teriparatide were detected with regard to patient body weight (39.5-120 kg in women; 47.6-128.9 kg in men).[1]

An increase in body weight was associated with an increase in volume of distribution. However, when normalized for body weight, volume of distribution was similar across the range of weights.[1]

Due to the change in volume of distribution, decreases in body weight were associated with increases in peak teriparatide concentration. The magnitude of these effects was not considered to be clinically relevant and teriparatide may be administered without regard to body weight.[1]

### Heart Failure

It is possible that patients with heart failure could have a reduction in teriparatide clearance due to a reduction in hepatic blood flow. However, because absorption from the subcutaneous tissue is the rate-limiting process that determines the duration of peptide exposure, it is unlikely that a reduction in teriparatide clearance would result in a clinically significant increase in the total systemic exposure.[1]

In the pivotal phase 3 study in PMW with osteoporosis, the incidence of adverse events was similar in patients with congestive heart failure compared with patients with normal cardiovascular function.[1]

## Other Factors

Smoking status and alcohol consumption do not appear to affect teriparatide disposition.[1]

## Drug Interactions

When teriparatide was administered to patients in the phase 3 trials taking beta blockers, calcium channel blockers, or hormone replacement therapy, population pharmacokinetic analyses did not identify any significant differences in the

- pharmacokinetics
- pharmacodynamics
- safety, or
- tolerability.[1]

## Pharmacokinetics and Calcium Pharmacodynamics in PMW With Osteoporosis

### Pharmacokinetics of Teriparatide (rhPTH[1-34]) and Calcium Pharmacodynamics in Postmenopausal Women With Osteoporosis

Pharmacokinetic samples from 360 PMW who participated in the Fracture Prevention Trial (FPT) were obtained and analyzed to determine the pharmacokinetics and serum calcium response to teriparatide.[3]

The participants received daily subcutaneous injections of teriparatide 20 µg or placebo for a median of 21 months. Teriparatide reached a maximum concentration ($C_{max}$) about 30 minutes after subcutaneous injection and then declined with a $T_{1/2}$ of 1 hour, resulting in a total duration of exposure of approximately 4 hours.[3]

The serum calcium concentration increased transiently, beginning approximately 2 hours after dosing and reaching a $C_{max}$ at 4.25 hours (median increase 0.4 mg/dL [0.1 mmol/L]). Calcium concentrations began to decline approximately 6 hours after dosing and returned to pre-dose levels by 16 to 24 hours after each dose.[3]

**Effects of Teriparatide in Japanese and Non-Japanese Populations: Bridging Findings on Pharmacokinetics and Efficacy**

Data from single teriparatide doses in healthy Japanese and Caucasian PMW, and in Japanese PMW with osteoporosis from a 6-month phase 2 dose-ranging study and from a 12-month phase 3 efficacy and safety study, were analyzed to determine pharmacokinetics in Japanese and Caucasian/non-Japanese subjects.[4]

Following completion of the FPT and prior to the design of dose-ranging and efficacy studies in Japanese subjects, a pharmacokinetic study (unpublished) was conducted comparing teriparatide pharmacokinetics following acute dosing in healthy Caucasian or first-generation Japanese PMW. In healthy PMW, the pharmacokinetics of teriparatide 40 µg was compared between Japanese (n=18) and Caucasian (n=15) subjects.[4]

The AUC and $C_{max}$ were approximately 30% to 40% higher in Japanese women compared to their Caucasian counterparts. However, body weight-adjusted values were comparable between both populations.[4]

The pharmacokinetic findings for Japanese PMW with osteoporosis appeared to be similar to those for healthy Japanese PMW and were also consistent with analyses of pharmacokinetic data from the FPT.[4]

**Effects of a Single Injection of Teriparatide on Bone Turnover Markers in Postmenopausal Women**

Another study evaluated single-dose teriparatide pharmacokinetics in 30 Japanese PMW with osteoporosis, with equal numbers in the placebo, 28.2-µg dose, and 56.5-µg dose treatment groups.[5]

The plasma concentration of teriparatide increased in a dose-dependent manner; $C_{max}$ was achieved 1 hour after the injection in both the 28.2-µg and 56.5-µg groups and the teriparatide concentration disappeared 6 hours after the injection.[5]

Serum-corrected calcium increased rapidly, reached its peak value 4 to 6 hours after administration, and returned to baseline 24 hours after administration.[5]

*Last Reviewed: 13-September-2022*

## ENCLOSED PRESCRIBING INFORMATION

FORTEO® (teriparatide injection), Lilly

## REFERENCES

*The published references below are available by contacting 1-800-LillyRx (1-800-545-5979).*

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