2.5 Clinical Overview

Product name:
TERIPARATIDE
20 micrograms/80 microliters
solution for injection in pre-filled pen

Drug Substance:
Teriparatide

Dosage Form, Strength:
Solution for injection, 20 µg/80 µL

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List of abbreviations

1,25(OH)2D	1,25 Dihydroxyvitamin D
25(OH)D	25-Hydroxyvitamin D
5-CNAC	8-(N-2-Hydroxy-5-Chloro-Benzoyl)-Amino-Caprylic Acid
ADR	Adverse Drug Reaction
AE	Adverse Event
ALN	Alendronate
ALP	Alkaline Phosphatase
API	Active Pharmaceutical Ingredient
ATC	Anatomical Therapeutic Chemical Classification
AUC	Area Under the Concentration-Time Curve
BfArM	Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte)
BMD	Bone Mineral Density
BMDD	Bone Mineral Density Distribution
BMI	Body Mass Index
BMP	Bone Morphogenetic Protein
BSAP	Bone Specific Alkaline Phosphatase
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CKD	Chronic Kidney Disease
C_{max}	Maximum concentration
CT	Computed Tomography
CTX	Type 1 Collagen Cross-Linked C-Telopeptide
CVD	Cardiovascular Disease
DANCE	Direct Analysis of Non-vertebral Fractures in the Community Experience
DKK	Dickkopf-Related Protein1
DNA	Deoxyribonucleic Acid
DXA	Dual-energy X-ray Absorptiometry
EC_{50}	Effective Concentration (50% of the maximum possible effect)
E. coli	*Escherichia coli*
EFOS	European Forsteo Observational Study
EMA	European Medicines Agency
EMBASE	Excerpta Medica dataBASE

EU	European Union
EUROFORS	European Study of Forsteo
ExFOS	Extended Forsteo Observational Study
e.g.	*exempli gratia* (for example)
eGFR	Estimated Glomerular Filtration Rate
EMBASE	Excerpta Medica dataBASE
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life Questionnaire (5 domains)
EQ-VAS	European Quality Visual Analogue Scale (overall health status)
EU	European Union
EFOS	European Forsteo Observational Study
FDA	Food and Drug Administration
FPR	Forteo Patient Registry
FRAX	Fracture Risk Assessment Tool
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GIO	Glucocorticoid-Induced Osteoporosis
GLP	Good Laboratory Practice
HCl	Hydrochloric Acid
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HSC	Haematopoietic Stem Cell
i.e.	*id est* (that means)
IGF-1	Insulin-Like Growth Factor-1
INN	International Nonproprietary Name
IU	International Units
i.v.	Intravenous(ly)
LS	Lumbar Spine
mRNA	Messenger Ribonucleic Acid
M-CSF	Macrophage Colony-Stimulating Factor
MEDLINE	Medical Literature Analysis and Retrieval System Online
MRI	Magnetic Resonance Imaging
MSC	Mesenchymal Stem Cell
NICE	National Institute for Health and Care Excellence (UK)
NSAID	Non-Steroidal Anti-Inflammatory Drug

NT-proBNP	N-terminal fragment of the pro-peptide of Brain Natriuretic Peptide
NTX	Amino-Terminal Cross-Linked Telopeptide Type 1 Collagen
ONJ	Osteonecrosis of the Jaw
OPG	Osteoprotegerin
OR	Odds Ratio
OGTT	Oral Glucose Tolerance Tests
pEC_{50}	Negative logarithm to base 10 of the EC_{50}
PICP	Procollagen I-Carboxyterminal Propeptide
PINP / P1NP	Procollagen Type I Amino-Terminal Propeptide
PL	Placebo
PTH	Parathyroid Hormone
PubMED	Public MEDLINE
QoL	Quality of Life
QUALEFFO	Quality-of-Life Questionnaire of the European Foundation for Osteoporosis
QCT	Quantitative Computed Tomography
r	Correlation Coefficient
RANK	Nuclear Factor Kappa-B
RANKL	Nuclear Factor Kappa-B Ligand
RCT	Randomised Controlled Trial
REMS	Risk Evaluation and Mitigation Strategy
RNA	Ribonucleic Acid
RR	Relative Risk / Risk Ratio
s.c.	Subcutaneous(ly)
SD	Standard Deviation
SEM	Standard Error of the Mean
SERM	Selective Oestrogen Receptor Modulator
SHOTZ	Skeletal Histomorphometry On Teriparatide or Zoledronic Acid
SmPC	Summary of Product Characteristics
SUCRA	Surface Under Cumulative Ranking Curve
T2D	Diabetes Mellitus Type 2
TBS	Trabecular Bone Score
TGFβ	Transforming Growth Factor Beta
TN	Treatment-naive
TNF	Tumour Necrosis Factor

TPTD	Teriparatide
$t_{1/2}$	Half-life
TOXNET	Toxicology Data Network
TGFβ	Transforming Growth Factor Beta
UK	United Kingdom
US	United States of America
USP	United States Pharmacopoeia
VAS	Visual Analogue Scale
VEGF-C	Vascular Endothelial Growth Factor
VERO	VERtebral fracture treatment comparisons in Osteoporotic women
vs.	Versus
VTE	Venous Thromboembolism
WHO	World Health Organization
WMD	Weighted Mean Difference

2.5.1 Product development rationale

This Clinical Overview provides a comprehensive review on the safety and efficacy of teriparatide based on a bibliographic appraisal of data on medicinal products containing teriparatide and authorised in the indications claimed by the applicant. The legal basis for this application refers to Article 10(1) of Directive 2001/83/EC - relating to applications for generic medicinal products.

Teriparatide contained in the product under discussion is manufactured by chemical solid phase peptide synthesis, whereas in the reference medicinal product Forsteo, teriparatide is produced in *Escherichia coli* (*E. coli*) based on recombinant DNA technology. The clinical performance of teriparatide is irrespective of the mode of synthesis and products containing chemically synthesised as well as recombinant teriparatide have gained approval in the European Union (G2, G3, G5)

Teriparatide, also referred to as recombinant human parathyroid hormone (1-34) (PTH [1-34]), was first approved in the United States in November 2002 (brand name: Forteo) for the treatment of osteoporosis in adult women and men. It was first introduced into the European pharmaceutical market in April 2003 (brand name: Forsteo).

The product Forsteo was first authorised for *Treatment of established osteoporosis in postmenopausal women*; the indication was extended to *Treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture* in June 2007 and again extended to include *Treatment of glucocorticoid-induced osteoporosis* in February 2008 (G2, G3, G4)

The document aims to provide concise and up-to-date information on teriparatide. The overview addresses the recently published literature on teriparatide and teriparatide containing medicinal products (up to July 2018) relevant for the claimed indications allowing for any new information on the safety and efficacy of teriparatide to be taken into account. Thereby, the overview demonstrates that the proposed summary of product characteristics (SmPC, G1) adequately reflects the prevailing scientific knowledge on teriparatide in the indications claimed by the applicant.

2.5.1.1 Pharmacological class

Teriparatide belongs to the pharmacotherapeutic group "Calcium homeostasis, parathyroid hormones and analogues (Anatomical Therapeutic Chemical Classification System (ATC) Code H05AA02)".

Teriparatide is a chemically synthetized 1-34 N-terminal fragment of endogenous human parathyroid hormone; the peptide is produced by standard solid phase peptide synthesis technology. The theoretical monoisotopic mass of teriparatide is 4115.1309 Dalton ( ). The amino acid sequence is: [1].

[1]

Figure 1: Human parathyroid hormone consists of 84 amino acids. Teriparatide represents the N-terminal portion of the first 34 amino acids (18)

As an active fragment of the human parathyroid hormone, teriparatide stimulates bone formation and used to treat osteoporosis. The recommended dose of teriparatide is 20 µg administered once daily by subcutaneous (s.c.) application. In patients with inadequate dietary intake of calcium and vitamin D, supplements are recommended. Further details on the posology and the method of administration are provided in the proposed SmPC for the product under discussion (G1).

2.5.1.2 Targeted indications

The product under discussion is indicated in adults for treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture as well as for treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture (G1).

2.5.1.3 Scientific background

The 84-amino acid native parathyroid hormone (PTH) (1-84) is the principal regulator of calcium homeostasis in mammals. PTH is released when calcium levels decrease, and it is suppressed when calcium levels increase. The hormone regulates bone metabolism: It stimulates 1-alpha-hydroxylase activity in the kidneys, thereby increasing serum 1,25-dihydroxyvitamin D levels, which promotes intestinal calcium absorption (73).

Teriparatide is the international non-proprietary name (INN) for the biologically active 34-amino acid N-terminal fragment of PTH (1-84). In early studies it was named (recombinant) PTH (1-34). Synthetic and genetically engineered versions of teriparatide both exist, sharing identical affinity for the human PTH surface receptors as well as possessing the same biological activity. Recombinant teriparatide contains no amino acid substitutions or chemical modifications and differs from the synthetic peptide only in its method of production and

purification. Recombinant teriparatide, as a consequence of its method of production, contains no glycosylation or other post-translational modifications (G2).

Bone remodelling

As shown in Figure 2, bone is constantly remodelled in the adult skeleton by the coordinated and sequential actions of bone-resorbing osteoclasts and bone-forming osteoblasts. These cells act to repair microdamage and to adapt bone structure to the mechanical and metabolic needs. Osteocytes, which represent > 95% of all bone cells, regulate bone remodelling. Osteoblasts are derived from mesenchymal stem cells (MSCs) and are specialised to produce an extracellular bone matrix, including type I collagen and non-collagenous proteins, including osteocalcin, osteonectin and osteopontin. The bone matrix is subsequently mineralised and stiffened by deposition of calcium hydroxyapatite; about 95% of the body's calcium is incorporated into the bone matrix. Osteoclasts are derived from haematopoietic stem cells (HSCs) of the macrophagic and monocytic lineage. Differentiation from precursor cells towards activated multinucleated cells is crucially dependent on receptor activator of nuclear factor-kappa B (RANK) ligand (RANKL) that acts on osteoclastic protein RANK, and permissive levels of macrophage colony-stimulating factor (M-CSF). RANKL is mainly produced by osteoblastic lineage cells (MSCs, osteoblasts and osteocytes) and lymphocytes. Mature bone-resorbing osteoclasts are large multinucleated cells. Using a sealing zone to attach at the bone surface and augmenting their surface with a ruffled border, mature osteoclasts secrete hydrochloric acid (HCl) to create an acidic microenvironment where enzymes such as cathepsin K, which degrades type I collagen, are most active (21, 73, 85).

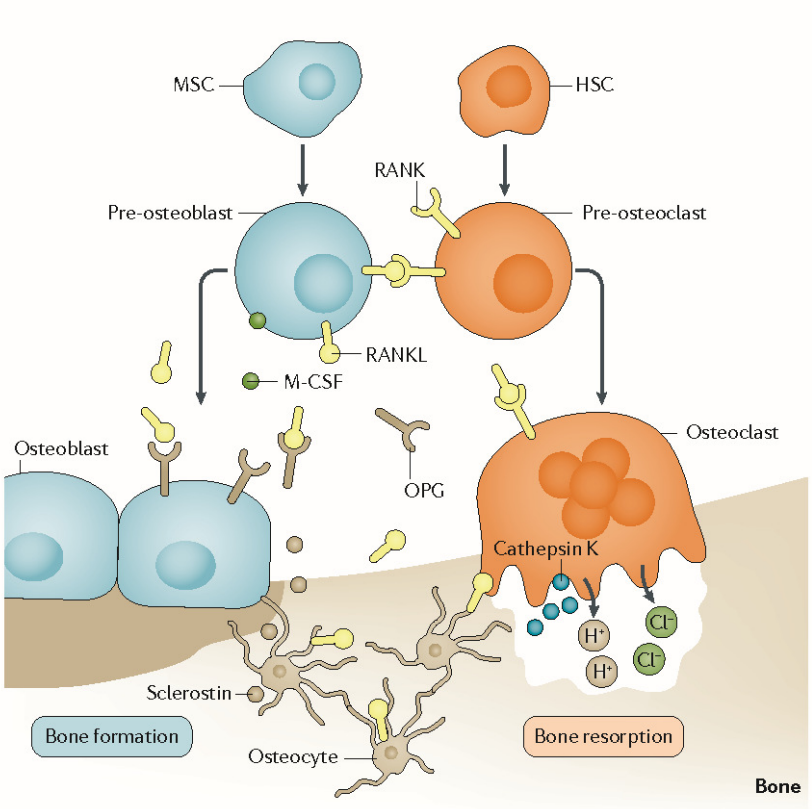

Figure 2: Bone remodelling according to Eastell et al. (2016) (21)

The absorption and distribution of calcium to the skeleton is under endocrine control of vitamin D, PTH and sex steroids, including oestrogens. The levels of PTH increase with age, which might partly be because of vitamin D insufficiency, and contribute to the increase in bone turnover with ageing (21).

Osteoporosis

Osteoporosis, from the Greek term "porous bone," is the most common bone disease, affecting millions of people worldwide. Osteoporosis is characterised by low bone mass, microarchitectural disruption and increased skeletal fragility, resulting in decreased bone strength and increased risk of fracture (72, 85). Many individuals with osteoporosis are not diagnosed with the disease until fragility fractures occur (4). Fragility fractures are defined as fractures that occur following a fall from standing height or less or with no trauma. The most common sites of fragility fracture are the spine (vertebral compression fractures), hip and wrist. Fragility fractures may also occur at the humerus, rib and pelvis (72, 85). Subsequent to the event of fracture, there is a considerable impact on health-related quality of life and related health costs (4).

Osteoporosis is a serious public health concern worldwide because of the morbidity and mortality associated with fragility fracture which is expected to affect a large proportion of people (40 - 50% of women and 13 - 22% of men) over the age of 50 years. In 2010, osteoporosis was estimated to affect 27.6 million people in Europe (9).

In particular, osteoporotic fractures are a major cause of morbidity in the population. Hip fractures cause acute pain and loss of function, and nearly always lead to hospitalisation. Recovery is slow, and rehabilitation is often incomplete, with many patients permanently institutionalised in nursing homes. Vertebral fractures may cause acute pain and loss of function but may also occur without serious symptoms. It is widely recognised that osteoporosis and consequent fractures are associated with increased mortality. In 2010, the number of deaths causally related to osteoporotic fractures was estimated at 43,000 in the European Union (EU). Approximately 50% of fracture-related deaths in women were due to hip fractures, 28% to clinical vertebral and 22% to other fractures. In Europe, osteoporosis accounted for more disability and life years lost than rheumatoid arthritis, but less than osteoarthritis. With regard to neoplastic diseases, the burden of osteoporosis was greater than for all sites of cancer, with the exception of lung cancers (40).

Based on data from the year 2010, 3.5 million new fragility fractures occur annually in Europe and more than 2 million in the United States (US) (8, 72). According to data collected for Europe, the most common fractures concern the hip (610,000 hip fractures), distal forearm (560,000 forearm fractures) and the spine (520,000 vertebral fractures). There is a significant economic burden associated with these injuries as they often require hospitalisation and long-term nursing care. Given the ageing population in Western countries, costs are expected to increase over the next decades (72, 73).

Primary osteoporosis

Primary osteoporosis is mostly associated with age and sex hormone deficiency; a genetic predisposition may also play a role. Sometimes, postmenopausal osteoporosis is referred to as type I since accelerated bone loss begins with the start of menopause. Senile osteoporosis, named type II, is related to the aging process and includes a decrease in the gastrointestinal absorption of calcium as well as a decreased rate of vitamin D activation. Osteoporosis type I

and II may be difficult to distinguish as causes and pathological processes merge with advancing age (21, 85).

Age-related osteoporosis results from the continuous deterioration of the trabeculae in bone. In addition, the reduction of oestrogen production in postmenopausal women causes a significant increase in bone loss. In men, sex-hormone-binding globulin inactivates testosterone and oestrogen as aging occurs, which may contribute to the decrease in bone mineral density (BMD) with time. Secondary osteoporosis is caused by several comorbid diseases and/or medications (21, 85).

Osteoporosis is mostly perceived associated with older women affected by postmenopausal hormone deficiency. However, osteoporotic fractures are also a leading cause of morbidity and mortality among aging men. About 30% of all hip fractures occur in men, and mortality resulting from fractures of the spine is significantly higher in men than in women. Like in women, hypogonadism is also the best documented risk factor for developing osteoporosis in men. In older men, testosterone levels are negatively correlated with the risk of fractures, and it seems that this age-related testosterone deficiency should not be considered as one of the many causes of secondary osteoporosis, rather one of the major and most important mechanisms of senile osteoporosis. Acute hypogonadism induced by ablation treatment for prostate cancer (surgical or pharmacological castration, antiandrogen therapy) is associated with an extremely high risk of fracture. Contributing factors include cigarette smoking, alcohol abuse and diseases that require corticosteroid treatment. Not all medications authorised for the treatment of postmenopausal osteoporosis are also indicated for the treatment of osteoporosis in men, and others have not been the subject of long-term and costly clinical trials required for such registration. Among drugs associated with BMD increases as well as risk reduction of new fractures in men are zoledronic acid, risedronate, teriparatide and denosumab (61).

Glucocorticoid-Induced Osteoporosis

Several diseases have been implicated in osteoporosis; they generally involve mechanisms related to the imbalance of calcium, vitamin D and sex hormones. For example, Cushing's syndrome has been found to accelerate bone loss through excess glucocorticoid production. In addition, many inflammatory diseases, such as rheumatoid arthritis, may require the patient to be on long-term glucocorticoid therapy. Notably, glucocorticoids are considered the most common medications linked to drug-induced osteoporosis (7, 85).

Because glucocorticoid receptors are present on both osteoclasts and osteoblasts, bone tissue is a target for glucocorticoids. The net effect of interaction with several pathways results in more osteoclast precursors and more mature osteoclasts. In addition, long-term treatment with glucocorticoids leads to enhanced apoptosis of osteoblasts and osteocytes, and subsequently a reduction in bone strength and bone loss (19).

It is estimated that 1% of the US population is treated long-term with glucocorticoid therapy; similar numbers may be assumed for European countries. About 10% of patients who receive long-term glucocorticoid treatment are diagnosed with a fracture, and 30 - 40% have radiographical evidence of vertebral fractures. The highest rate of bone loss occurs within the first 3 - 6 months of glucocorticoid treatment, and a slower decline continues with persistent use. Generally, when glucocorticoids are terminated BMD increases and fracture risk declines (7).

Screening and diagnosis

Published osteoporosis screening guidelines vary greatly. It is mostly recommended that adults older than 50 years of age with a history of fragility fracture receive regular BMD screening. The US Preventive Services Task Force recommends BMD screening for all women 65 years of age and older and for younger women with equivalent or greater fracture risk. A number of studies documented benefit of screening for early detection of osteoporosis. However, there is a lack of consistent evidence from randomised controlled trials (RCTs) regarding the recommended optimal frequency of BMD monitoring (85).

Numerous screening methods are employed. The gold standard for diagnosing osteoporosis utilises BMD measurements, especially in the hip and lumbar spine with dual-energy x-ray absorptiometry (DXA). Resulting T-scores are used to interpret BMD and to correlate results with fracture risk; i.e. a low BMD (or a highly negative T-score, see also Table 1) is strongly correlated with a high fracture risk (72, 85). Another commonly used tool for BMD measuring is quantitative computed tomography (QCT) (62). According to World Health Organization (WHO) criteria, osteoporosis is defined as a BMD T-score of 2.5 standard deviations (SD) or more below the average for young, healthy, premenopausal women (equating to a T-score of less than or equal to –2.5 [a normal T-score is greater than –1]) (4).

Table 1: T-Scores and World Health Organization (WHO) Diagnostic Criteria for Osteoporosis (4, 85)

T-Score	Interpretation
-1.0 and higher	Normal
-1.0 to -2.5	Osteopenia
-2.5 and lower	Osteoporosis
-2.5 and lower, with ≥ one or more fragility fractures	Severe osteoporosis

The Fracture Risk Assessment Tool (FRAX) is another diagnostic instrument, developed in Great Britain. It takes into account risk factors such as age, race, alcohol use, gender, body mass index (BMI), smoking history, prior personal or parental history of fracture, use of glucocorticoids, secondary osteoporosis, rheumatoid arthritis and femoral neck BMD measurements to predict the 10-year probability of hip fracture and other major osteoporotic fracture (36, 72, 85).

Management and pharmacological treatment options

The treatment of osteoporosis consists of lifestyle modifications and pharmacologic therapy. An example for current recommendations is shown in Figure 3. Lifestyle adjustments include adequate vitamin D and calcium intake, a balanced diet, weight control, exercise, smoking cessation, counselling on fall prevention and avoidance of heavy alcohol use (7, 9).

Supplementation with calcium and vitamin D has a significant role in osteoporosis management but is not sufficient to reduce fracture risk. The recommendations for dietary vitamin D intake are based on the benefits of the combination of calcium and vitamin D to skeletal health; there is no evidence supporting a benefit of vitamin D supplementation alone (72).

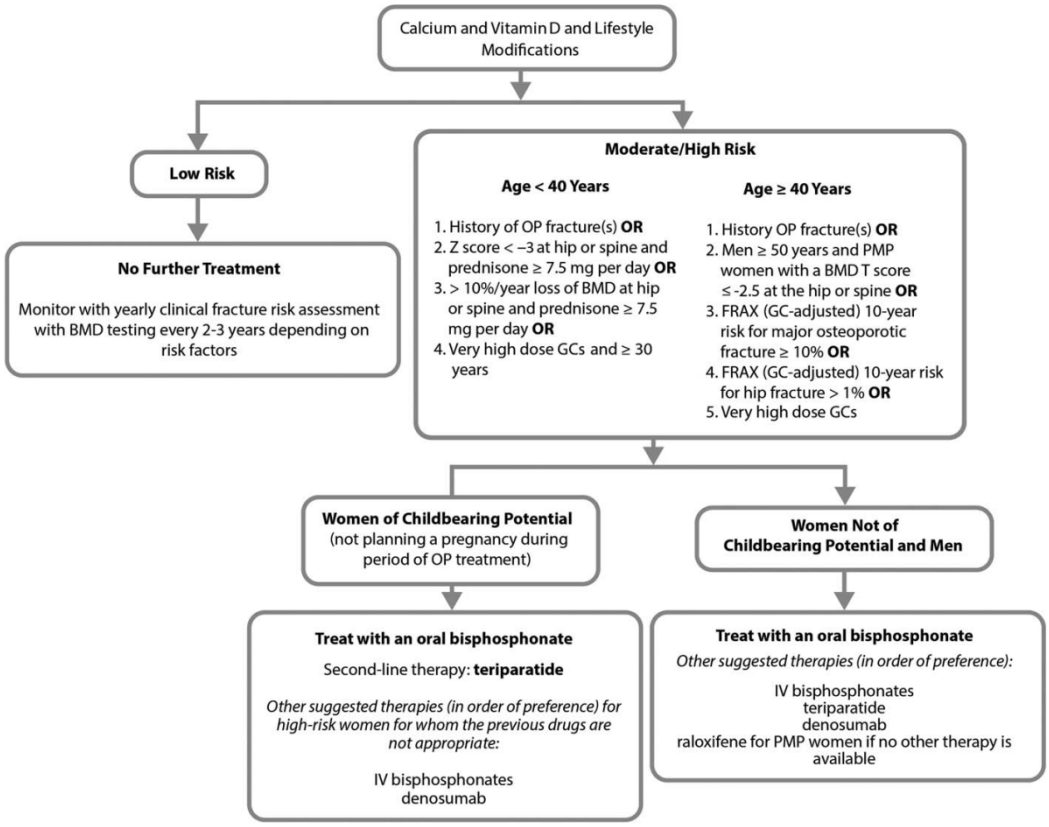

Figure 3: Recommendations for the treatment of glucocorticoid-induced osteoporosis according to the American College of Rheumatology Guideline (2017) (7)

The goal of pharmacological therapy is to reduce the risk of fractures. Guidelines provide directions for clinicians and affected patients making treatment decisions. Patients' age and comorbidities as well as preferences need to be taken into account as they may affect compliance (7, 9).

Medications to treat osteoporosis are categorised as either antiresorptive (i.e. bisphosphonates, oestrogen agonist / antagonists, oestrogens, calcitonin and denosumab) or anabolic (i.e. teriparatide). Antiresorptive medications primarily decrease the rate of bone resorption while anabolic medications increase bone formation more than bone resorption (85).

Generally, guidelines recommend bisphosphonates (e.g. alendronate, risedronate and zoledronic acid) as a first-line option for the prevention and/or treatment of osteoporosis in postmenopausal women, men and/or patients treated with long-term glucocorticoids. Bisphosphonates inhibit bone resorption by selective adsorption to mineral surfaces and subsequent internalisation by bone-resorbing osteoclasts where they interfere with various biochemical processes. They can be administered orally or intravenously. Extended-interval dosing, such as once weekly or monthly, is possible due to the long half-lives of these agents. Bisphosphonates are excreted by the kidneys; thus, toxicities may occur from accumulation in patients with renal impairment. Rarely, bisphosphonates may evoke osteonecrosis of the jaw (ONJ) or atypical femur fractures. Continued treatment is needed but since bisphosphonates may accumulate in bone and continue to be released for months or years after treatment

cessation, treatment interruptions or 'drug holidays' can be considered in appropriate patients (72, 76, 85).

Denosumab was the first biologic agent available for treatment of osteoporosis. It is a fully human monoclonal antibody to the receptor activator of nuclear factor kappa-B ligand (RANKL), a member of the tumour necrosis factor (TNF) receptor superfamily essential for osteoclastogenesis. RANKL is a transmembrane protein required for the formation, function and survival of osteoclasts. Denosumab prevents the interaction between the protein and its receptor RANK, thereby decreasing bone resorption in cortical and trabecular bone. The antibody is currently authorised for treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. It is administered as a single subcutaneous injection once every 6 months. Denosumab is well tolerated, but reported adverse effects include hypersensitivity, serious infections, dermatological reactions, musculoskeletal pain and hypercholesterolemia. Rare cases of ONJ and atypical femur fractures have also been reported. As denosumab can cause hypocalcaemia, calcium levels need to be corrected prior to treatment initiation (72, 76, 85).

Due to the overall health risks exceeding benefits, hormonal replacement therapy is no longer recommended as first line for the treatment and prevention of osteoporosis in postmenopausal and premenopausal women. Clinical trials such as the Women's Health Initiative demonstrated that treatment of postmenopausal patients with an oestrogen-progestin combination resulted in a statistically significant reduction in fractures; however, an increase in the risk of cardiovascular events, stroke, venous thromboembolism (VTE) and invasive breast cancer was observed (72, 85).

For osteoporotic men at high risk of fracture, the US based Endocrine Society recommends combination use of anti-fracture treatment with testosterone therapy. Testosterone monotherapy is recommended either for those in whom antiosteoporotic therapy is contraindicated and whose testosterone levels are less than 200 ng/dL or for those at borderline high risk for fracture who have serum testosterone levels less than 200 ng/dL and have signs or symptoms of androgen deficiency or hypogonadism (85).

Hormonal therapies of osteoporosis include the selective oestrogen receptor modulator (SERM) raloxifene which exhibits dual agonistic and antagonistic properties. Raloxifene acts as an oestrogenic agonist on the bone by decreasing bone resorption and bone turnover, thus increasing BMD. It also has oestrogen antagonistic activity on breast and uterine tissue. The medication is in particular considered in women with an increased risk of vertebral fractures who may be at risk for developing breast cancer. Raloxifene is orally dosed at 60 mg per day.

Adverse events included vaginal bleeding, hot flashes, worsening of pre-existing hypertriglyceridaemia, VTE and an increased risk for cardiovascular disease. Bazedoxifene is a tissue selective oestrogen complex. The active ingredients of conjugated oestrogens are primarily the sulphate esters of oestrone, equilin sulphates and 17α/β-oestradiol. These substitute for the loss of oestrogen production in menopausal women, and alleviate menopausal symptoms. As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of bazedoxifene, acting as an oestrogen receptor antagonist in the uterus, greatly reduces the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women. The medication is orally dosed once daily. Adverse events are similar to other oestrogen-containing medications (72, 85).

Calcitonin is a synthetic polypeptide hormone with properties similar to natural calcitonin found in mammals. The effects of calcitonin on normal human bone physiology are unclear; however, calcitonin receptors have been discovered on osteoclasts and osteoblasts. Calcitonin preparations have been approved for example by the US Food and Drug Administration (FDA) but given the limited efficacy of calcitonin in fracture prevention relative to other available agents and concerns about an increased risk of cancer with long-term calcitonin use, it is now rarely used for osteoporosis prevention or treatment (44).

The PTH analogue teriparatide is the first anabolic treatment approved for osteoporosis. It mimics the physiological actions of PTH in stimulating new bone formation on the surface of bone by stimulating osteoblastic activity when given intermittently at small doses. As teriparatide is the active agent under discussion here, its mode of action as well as its pharmacokinetic and pharmacodynamic characteristics, efficacy and safety profile will be discussed in detail in the following sections of this Clinical Overview.

Currently investigated drugs for the treatment of osteoporosis include abaloparatide, another recombinant human PTH analogue; clinical studies demonstrated a similar effect to teriparatide regarding the increase of BMD (31). Abaloparatide has gained approval in the US in the year 2017 but marketing authorisation was not granted in the EU based on insufficient data documenting a positive benefit-risk balance. Romosozumab is a humanised monoclonal antibody that inhibits the protein sclerostin which is secreted by osteoclasts to reduce bone formation by interfering with the proliferation and function of osteoblasts. Its efficacy has been demonstrated in RCTs but it may evoke serious adverse cardiovascular events. Lasofoxifene, a third-generation SERM, demonstrated a risk reduction in both vertebral fractures and non-vertebral fractures in RCTs. It was approved in the EU in the year 2009 but authorisation expired in 2012 based on the sunset clause (85). Strontium ranelate, which improved BMD via promotion of osteoblast activity, was recently withdrawn because of concerns about the risk of thromboembolism and cardiovascular events (15).

Dede and Callan (2018) recently reviewed current guidelines on the management of osteoporosis. Overall, European guidelines recommend initial therapy with alendronate, risedronate and denosumab. Parenteral administration of teriparatide, denosumab or zoledronic acid may be an appropriate initial therapy for patients unable to use oral therapy. According to the United Kingdom (UK) National Institute for Health and Care Excellence (NICE 2018), oral bisphosphonates are the first-line options for osteoporosis in adults who are eligible for fracture risk assessment and where the 10-year probability of osteoporotic fragility fracture is at least 1%, as calculated either by FRAX or QFracture. Intravenous bisphosphonates should be used when oral bisphosphonates are contraindicated or not tolerated. Denosumab is recommended for primary prevention of fracture in postmenopausal women who are at increased risk of fractures, when oral bisphosphonates are contraindicated or not tolerated and who meet a threshold of a combination of age, low T-score and clinical risk factors. Teriparatide is recommended for secondary prevention in postmenopausal women, 65 years or older, who meet specific thresholds of T-score and clinical risk factors, when oral bisphosphonates are contraindicated or not tolerated or when response to treatment with alendronate or risedronate has been unsatisfactory. The same applies for raloxifene which can be considered for secondary prevention in women who are not able to receive oral bisphosphonates and meet a threshold of a combination of age, low T-score and clinical risk factors (14, 72).

Summarised, osteoporosis is a metabolic bone disease characterised by low bone density and deterioration of bone architecture that enhance the risk of fragility fractures. Osteoporosis-

related fractures can increase pain, disability, nursing home placement, health care costs and mortality. The diagnosis of osteoporosis is primarily determined by measuring BMD using non-invasive imaging methods, for example dual-energy x-ray absorptiometry or quantitative computed tomography. Beside lifestyle modifications as well as adequate calcium and vitamin D intake, treatment options for osteoporosis include orally or intravenously applied bisphosphonates, receptor activator of nuclear factor kappa-B ligand inhibitors, oestrogen agonists / antagonists, parathyroid hormone analogues and calcitonin. While professional organizations have compiled recommendations for targeting different patient populations, a consensus has yet to be developed. Depending on regional guidelines, teriparatide is mentioned among first-line or second-line therapy options in the treatment of osteoporosis and the prevention of fragility fractures.

2.5.1.4 Clinical development program

Seminal observations by the American endocrinologist Fuller Albright in the 1940s established the key role for oestrogen in regulating bone metabolism in women, and oestrogen was subsequently found to also have an important role in the male skeleton. Oestrogen treatment is effective in both the prevention and treatment of osteoporosis. As revealed by the Women's Health Initiative including more than 16,000 postmenopausal women, oestrogen substitution significantly increased BMD and reduced the risk of fracture; however, it increased the risk of cardiovascular events and breast cancer (44, 72, 76, 85).

The development of teriparatide may also be traced back to Fuller Albright who made the clinical observation that chronic parathyroid hormone excess caused marked bone loss due to increased bone resorption, but it was also associated with an increase in bone formation (44). Findings from studies with animals and humans subsequently showed that, in contrast to continuous exposure, intermittent exposure of bone to parathyroid hormone increased bone formation with smaller increases in bone resorption, resulting in a net anabolic effect (18). First clinical observations on the treatment of osteoporosis with a fragment of PTH date back to the late 1970s. Reeve et al. (1980) reported that in 21 women with osteoporosis administration of synthetic human PTH fragment (1-34) over 6 - 24 months significantly increased the iliac trabecular bone volume (74). However, concerns about possible cortical bone loss and hypercalcaemic side effects postponed larger clinical studies; findings from the first placebo-controlled trial were published in the year 2001, confirming a significant increase in trabecular bone mass and showing also an important increase in cortical bone. Eli Lilly and Company conducted a formal registration trial in postmenopausal women with osteoporosis. The unexpected occurrence of osteosarcomas in Fisher 344 rats treated long-term with teriparatide provoked an abrupt cessation of that trial. However, ambiguity concerning the relevance of this rat finding to human disease, combined with significant anti-fracture efficacy, led to the approval of teriparatide for postmenopausal women and for men with osteoporosis "at high risk for fracture" in the year 2002 in the US and in 2003 in the EU. Subsequently, teriparatide has been approved also for treatment of patients with glucocorticoid-associated osteoporosis, and more recently, publications indicating utility of this agent for dental and orthopaedic applications have begun to appear (18, 55).

Currently, teriparatide has been authorised in countries worldwide, including the EU, the US, Canada, Japan, China and India. Besides the originator product (Forsteo / Forteo) marketed by Eli Lilly and company, several biosimilars of teriparatide have been approved (for example Terrosa and Movymia in the EU in 2016). Next to that, approval has also been granted to

products containing chemically synthetized teriparatide (e.g. Teriparatid-ratiopharm in 2017, G5).

2.5.1.5 Concordance with current standard research approaches

There are different therapeutic strategies to treat osteoporosis and to prevent fragility fractures. As stated in detail in section 2.5.1.3, recent guidelines, aside from adequate calcium and vitamin D intake, and (if applicable) lifestyle modifications, name orally or intravenously applied bisphosphonates, receptor activator of nuclear factor kappa-B ligand inhibitors, oestrogen agonists / antagonists, parathyroid hormone analogues and calcitonin as treatment options. Consequently, for the evaluation of the efficacy and safety of teriparatide in the indications claimed by the applicant, the active ingredient of the product under discussion has been intensively investigated for its effects, using appropriate study designs and validated analytical methods.

Search strategy
In order to obtain a complete and current update on the published literature, searches in a variety of classified databases were performed (as of July 2018). As regards the literature search strategy (both for the active substance and the excipients), relevant guidelines and publications were identified in an extended, timely unlimited search of the scientific databases MEDLINE (published by the US National Library of Medicine) and TOXNET. In addition, the internet was searched (search terms including 'teriparatide', 'osteoporosis' and 'prevention of fragility fractures') for relevant scientific literature such as currently applicable guidelines of medical societies. Furthermore, assessment reports and scientific discussions on teriparatide published by regulatory authorities were considered, when applicable.

The screening and selection of literature from MEDLINE was conducted without restrictions using the term 'teriparatide'. The resulting hits were evaluated via assessment of the abstract (when no abstract had been available, the header was screened) for possible relevance on preclinical and clinical aspects (i.e. pharmacology, pharmacokinetics, toxicology, efficacy and safety). Based on this evaluation, potentially relevant publications were selected, generally assessed based on the ordered full texts, and relevant references were included and discussed in Module 2.4 or Module 2.5, as applicable.

Good Clinical Practice
It may be assumed that the vast majority of research on teriparatide that led to the worldwide authorisation of originator product (Forsteo / Forteo) and other teriparatide containing medicinal products adhered to the principles of Good Clinical Practice (GCP) and Good Laboratory Practice (GLP). Even if not all studies presented and evaluated in this Clinical Overview obeyed to GCP and GLP guidelines in all details, this is not expected to affect the overall conclusions of the document.

2.5.2 Overview of biopharmaceutics

To demonstrate the similarity of the product under discussion to the reference product, the following considerations have been made:

1) The active pharmaceutical ingredient (API) manufactured by chemical synthesis is a well-controlled peptide fulfilling all the criteria as set forth in the USP monograph. Impurities observed are well identified and do not lead to concern.
2) The formulation of product and the reference product Forsteo have exactly the same qualitative and quantitative composition with regard to API and excipients.
3) Equivalence was demonstrated for the identity, amino acid sequence, and structure for the API contained in both formulations (teriparatide formulation and Forsteo). Therefore, the API in the applied formulation manufactured by chemical synthesis is considered to be the same active substance as used in reference product Forsteo, which is obtained by recombinant technology. In addition, the impurity profile and degradation profile of both formulations are equivalent.
4) Both formulations have a comparable biological activity based on the determined effective concentration (pEC_{50}) level.
5) Both formulations are presented in the same pharmaceutical dosage form, i.e. an aqueous solution for injection. The route of administration to patients for both is the same, i.e. subcutaneous injection. Consequently, no differences in the performance of the two dosage forms, in particular the release of the API from the dosage form to its target compartment - or its surrogate sampling compartment, the blood circulation and its biological action- are expected.
6) The applied indication and dose regimen for both, teriparatide formulation and reference product Forsteo is identical.

Based on these considerations, no further in-vivo characterization in terms of bioavailability have been performed (see module 3.2.P.2.2.3).

2.5.3 Overview of clinical pharmacology

Of note, particularly in early studies starting in the 1980s up to the early 2000s, teriparatide was referred to (recombinant human) PTH (1-34). In this document, the designation teriparatide is used throughout.

2.5.3.1 Pharmacokinetics

The recommended posology is 20 µg teriparatide administered once daily by subcutaneous (s.c.) injection in the thigh or abdomen. The maximum total duration of treatment should be 24 months as a single course over a patient's lifetime (G1).

Satterwhite et al. (2010) examined the pharmacokinetics and resulting serum calcium response to teriparatide (20 µg/day, in comparison with placebo) in postmenopausal women with osteoporosis. Samples were obtained from 360 women dosed at months 1, 3, 6, 12 and 18 who participated in the Fracture Prevention Trial that randomly assigned 1637 women to 20 or 40 µg teriparatide or placebo. One blood sample was collected per patient at each study visit within prespecified sampling windows of 0 - 30 min, 30 min - 1 h, 1 - 2 h, 2 - 3 h and 3 - 4 h postdose. The teriparatide concentration - time profile is characterised by rapid absorption and elimination with an obvious monoexponential decline in concentrations (79).

After s.c. administration, teriparatide had an absolute bioavailability of 95%. The peptide reached a maximum concentration after about 30 min and then declined with a half-life of one

hour. This half-life reflects the time required for absorption from the injection site as the true elimination half-life following intravenous (i.v.) administration and was 5 min. In most subjects, teriparatide concentrations were < 50 pg/mL by 3 hours after injection of a 20-µg dose. The mean total duration of exposure to the peptide was about 4 hours.

It is estimated that peak molar concentrations of teriparatide briefly exceed the upper limit of normal for endogenous PTH (~65 pg/mL) by 4- to 5-fold for about 30 min postdose. The mean systemic exposure (endogenous PTH and teriparatide) over 24 hours does not exceed the upper limit of normal and is below the levels found in patients with mild hyperparathyroidism.

Of all covariates tested, only body weight and injection site were found to have small but statistically significant influences on the rate of teriparatide absorption. No association was found between age, smoking, alcohol history or renal function and teriparatide pharmacokinetics. The slower rates of absorption after administration to the thigh compared to the abdominal wall and in heavier patients did not affect the overall systemic exposure to teriparatide. Accompanying population pharmacodynamic analyses confirmed that the magnitude of the effects of body weight and injection site on the rate of teriparatide absorption, and the resultant peak serum concentrations, is not considered to be clinically meaningful.

Being a peptide hormone, teriparatide is metabolised by non-specific peptidases. Elimination occurs through hepatic and extra-hepatic clearance (approx. 62 L/hour in women and 94 L/hour in men). The volume of distribution is approx. 1.7 L/kg. Inter-subject variability in systemic clearance and volume of distribution is 25 - 50%.

Teriparatide transiently increased serum calcium, with the maximum effect observed at approx. 4.25 hours (median increase 0.4 mg/dL). Calcium concentrations returned to predose levels by 16 - 24 hours after each dose. Persistent hypercalcaemia was not observed. Hence, following a daily 20-µg dose, teriparatide produces a modest but transient increase in serum calcium, consistent with the known effects of endogenous PTH on mineral metabolism. The excursion in serum calcium is brief, due to the short length of time that teriparatide concentrations are elevated (79).

Pharmacokinetic data is also summarised in the scientific discussion published upon the authorisation of the originator product Forsteo (G2): Following s.c. injection, absorption of teriparatide is rapid with peak concentrations after 30 min and a half-life of approx. one hour and bioavailability of about 95%. Systemic exposure is approx. 20% to 30% lower in men than in women. In population analyses, volume of distribution increased from 21% to 30% when teriparatide was injected into the thigh relative to the abdominal wall. Studies in patients with mild to moderate heart failure or mild to moderate renal insufficiency suggested that dose adjustment is not required. There are no pharmacokinetic data for patients with impaired hepatic function (G2, G3) (73).

Renal impairment

Imai et al. (2014) investigated whether the pharmacokinetics of teriparatide are affected by renal impairment. Subjects were enrolled and grouped on the basis of renal function stratified as: normal function to mild renal impairment (estimated glomerular filtration rate [eGFR] $\geq$ 60.0 mL/min/1.73 m^2, n = 8) subjects), moderate impairment (eGFR: 30.0 - 59.9 mL/min/1.73 m^2, n = 5), and severe impairment (eGFR: 15.0 - 29.9 mL/min/1.73 m^2, n = 5). Pharmacokinetic parameters, blood and urine electrolytes concentrations and safety profiles were assessed following a single s.c. injection of teriparatide acetate (56.5 µg as

teriparatide). The elimination half-life ($t_{1/2}$) and the mean residence time extrapolated to infinity were significantly prolonged in the group with severe renal impairment ($t_{1/2}$: 5.0 hours) compared with normal to mild and moderate impairment groups ($t_{1/2}$: 1.5 hours and 1.2 hours, respectively). However, virtually all of the teriparatide was eliminated from the blood after 24 hours. In addition, there were no apparent problems concerning safety or tolerability. The authors concluded that with repeated administration, drug accumulation does not pose a problem in renally impaired patients. Administration every second day or once per week may be considered in patients with significantly impaired renal function (38).

Oral administration
Hämmerle et al. (2012) examined the single dose pharmacokinetic profile of oral teriparatide in combination with the peptide absorption enhancer 5-CNAC ([8-(N-2-hydroxy-5-chloro-benzoyl)-amino-caprylic acid]) in healthy postmenopausal women using a partially-blinded, incomplete crossover study design. Of 32 subjects enrolled, 16 were randomised to receive 4 single doses out of 6 different treatments: placebo, teriparatide 20 µg s.c. or 1, 2.5, 5 or 10 mg of PTH134 (i.e. oral teriparatide) formulated with 200 mg 5-CNAC. Subsequently, another 16 subjects were randomised to receive 4 out of 6 different treatments: placebo, teriparatide 20 µg s.c., or 2.5 or 5 mg of oral PTH134 formulated with either 100 or 200 mg 5-CNAC. Doses were given ≥ 6 days apart. All doses of PTH134 were rapidly absorbed and showed robust blood concentrations in a dose-dependent manner. Interestingly, teriparatide disappeared from blood faster after oral than after s.c. administration. Specifically, 2.5 and 5 mg PTH134 (containing 200 mg 5-CNAC) demonstrated maximum serum concentration (C_{max}) and area under concentration-time curve $(AUC)_{(0\text{-last})}$ values closest to those of s.c. teriparatide 20 µg. According to the authors, the study demonstrated potential therapeutically relevant teriparatide systemic exposure levels after oral administration of teriparatide formulated with the absorption enhancer 5-CNAC (34).

In summary, the daily administration of 20 µg teriparatide via s.c. application is characterised by rapid absorption (maximum concentration achieved within 30 min) and rapid elimination with a half-life of about one hour. The total duration of exposure to the peptide is approx. 4 hours; there is no evidence of accumulation. Teriparatide transiently increases serum calcium, with a maximum effect approx. 4 hours postdose. Calcium concentrations return to predose levels before the next dose when applied 24 hours apart. In pharmacokinetic studies, persistent hypercalcaemia was not observed. Pharmacokinetics are not significantly affected by mild to moderate renal impairment.

2.5.3.2 Drug interactions

Limited data are available on the use of teriparatide and other concurrent medications:

As teriparatide is metabolised by non-specific peptidases, it is unlikely to interfere with the metabolism of glucocorticoids which occurs by microsomal enzymes in the liver and other tissues, nor would its metabolism be altered by glucocorticoids. Most of the known glucocorticoid drug interactions are the results of either induction or inhibition of P450 enzymes whereas teriparatide and other peptides do not directly interact with the P450 metabolising system (G3).

One study analysed the coadministration of teriparatide and oral hydrochlorothiazide (25 mg) in 20 healthy subjects. Teriparatide at a dose of 40 µg did not affect serum calcium levels and no clinically significant interactions were noted (73) (G2).

A study enrolling 17 patients with mild, moderate or severe hypercalcemia and 9 healthy subjects did not find clinically significant increases in serum calcium with the coadministration of i.v. furosemide 20 to 100 mg daily and s.c. teriparatide 40 µg (73).

Because teriparatide can transiently increase serum calcium levels, caution should be exercised when concomitantly administering teriparatide and digitalis preparations. In 15 healthy subjects, the administration of teriparatide (40 µg, s.c.), added to digoxin at steady state, did not alter the effect of digoxin. It has been suggested that hypercalcaemia may predispose patients who are receiving digitalis to its toxicity, and caution and frequent monitoring are recommended (73).

Co-administration of raloxifene or hormone replacement therapy with teriparatide did not alter effects on serum or urine calcium nor predispose to clinically relevant adverse events (G1).

Although data is limited, there is currently no evidence for clinically relevant drug interactions involving teriparatide.

2.5.3.3 Pharmacodynamics

Anabolic versus antiresorptive effects
Anabolic agents such as teriparatide directly stimulate bone formation whereas antiresorptive agents (e.g., oestrogen, raloxifene, bisphosphonates and calcitonin) inhibit osteoclast-mediated bone loss and thus reduce bone turnover (73).

Mode of action
Endogenous PTH, an 84-amino acid peptide, plays a central role in calcium and phosphate metabolism in the bone and kidneys. Its physiological effects include stimulation of bone formation by directly affecting bone-forming cells (osteoblasts) and increasing renal tubular re-absorption of calcium and excretion of phosphate, and by indirectly increasing intestinal absorption of calcium via its effects on 1,25-dihydroxyvitamin D production. Teriparatide and PTH mediate their biological effects via specific, G-protein-dependent, high-affinity membrane cell-surface receptors which are expressed on osteoblasts and renal tubular cells; both these molecules bind to the receptors with the same affinity and exert the same physiological effects on bone and kidneys. It has been suggested that ligand binding induces a cascade that activates protein kinase-1, cyclic adenosine monophosphate, protein kinase C and phospholipase C. The activation of these pathways results in an increase in the number of active osteoblasts, a decrease in osteoblast apoptosis and probably, recruitment of bone lining cells as newly formed osteoblasts, thereby increasing bone strength, mass and diameter, and bone structural integrity, as well as increasing serum and urinary levels of markers of bone formation and resorption (33).

Based on a review of published data, Dore et al. (2013) summarised various possible effects of teriparatide on the bone (19). Therefore, teriparatide

- Increases levels of insulin-like growth factor 1, resulting in increases in the number of osteoblast precursors, and increases osteoblast survival

- Activates the calcium protein kinase C pathway that stimulates proliferation of cells in the osteoblastic lineage
- Increases the expression of Wnt signalling, resulting in increased bone formation
- Blunts the mRNA and protein expression of sclerostin, a Wnt antagonist, resulting in increased bone formation
- Controls the replication and differentiation and survival of osteoblast precursors by influencing the expression and release of fibroblast growth factor 2, interleukin 6, bone morphogenetic protein, and transforming growth factor beta
- Activates quiescent bone-lining cells
- Increases trabecular bone volume
- Decreases osteoblast apoptosis

Cumulatively, these effects are therapeutically beneficial in terms of increases in estimated bone strength of the spine, hip and peripheral anatomic sites as well as decreased fracture risk. Teriparatide administration stimulates bone resorption and formation in a dose-responsive fashion. Specifically, serum bone formation markers (and biopsy-documented bone formation rates) increase within weeks of the initiation of PTH analogue therapy while the increase in resorption markers are delayed (22, 33, 73).

In clinical studies, teriparatide-induced stimulation of bone formation peaked after 6 - 12 months of therapy, after which serum markers of both osteoblast and osteoclast activity slowly revert toward baseline levels. This waning of osteoblast stimulation may be one of the limiting factors in the clinical use of PTH analogues for longer periods. Moreover, studies investigating the effect of a second course of teriparatide therapy in men and postmenopausal women have suggested that the anabolic potential of teriparatide remains reduced even after a year 'drug holiday' (22, 28).

Effects of intermittent administration

The anabolic effectiveness of teriparatide requires that it be administered intermittently. In its clinical application as anabolic therapy, the peptide is applied by daily s.c. injection. Pharmacokinetic action required for this effect is a peak of circulating teriparatide that returns to control levels within few hours. Thus the anabolic effect of teriparatide has two components: A remodelling dependent effect said to account for over 70% and a modelling based effect accounting for the remaining 30% of the anabolic effect. Current views of the anabolic action of teriparatide are that it increases the recruitment and activation of basic multicellular units, acts on committed osteoblast precursors to promote their differentiation, inhibits osteoblast and osteocyte apoptosis and inhibits the production of the bone formation inhibitor, sclerostin. There is also much interest in the possibility that teriparatide treatment results in transient activation of osteoclasts that in turn produce activity that enhances the osteoblast differentiation effect. The latter may be independent of resorption or may result from the release of growth factors (transforming growth factor beta [TGFβ], insulin-like growth factor-1 [IGF-1]) in the resorption process that enhance the availability of mesenchymal stem cells (TGFβ), or their differentiation in the osteoblast lineage (IGF-1) (56). These aspects of the anabolic action of teriparatide (and accordingly of PTH) are summarised in Figure 4.

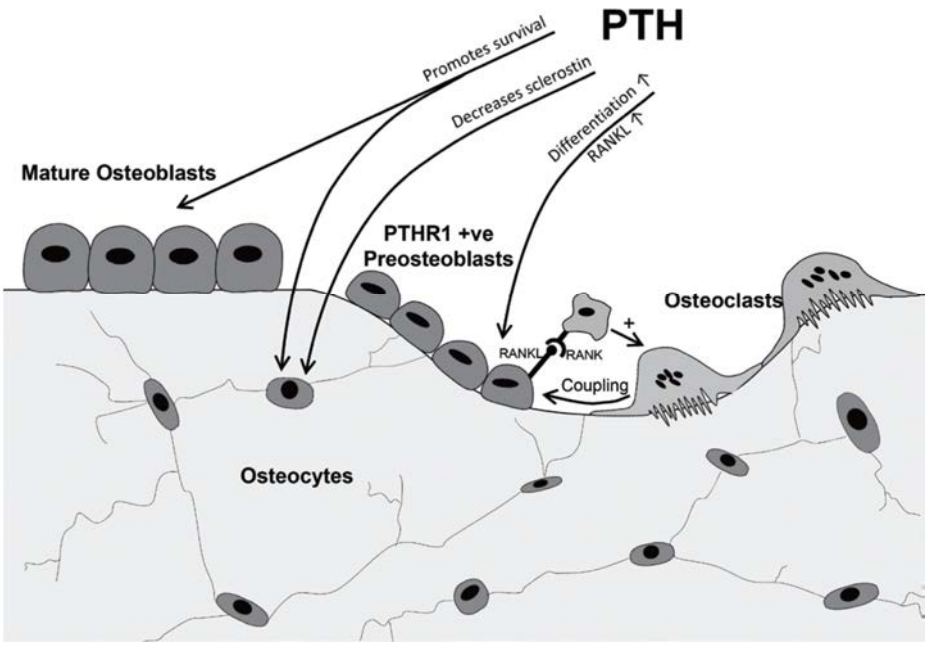

Figure 4: Anabolic action of intermittently used PTH and (accordingly of teriparatide) through remodelling. PTH promotes differentiation of committed osteoblast precursors, activation of osteoclasts that produce coupling activities, promotes survival of osteoblasts and osteocytes, and inhibits sclerostin production by osteocytes (56).

Effect of teriparatide on regulators of bone formation

Several bone turnover markers have been studied for monitoring response to teriparatide. The procollagen type I amino-terminal propeptide (PINP / P1NP) has proven to have the greatest 'signal to noise ratio', and so it is the most suitable marker. Bone formation markers increase within days of starting teriparatide and reach a peak between 6 and 12 months. They remain above baseline for the whole of the 24-month treatment period (22).

In an exploratory analysis, Fahrleitner-Pammer et al. (2016) assessed the effects of teriparatide on cancellous bone microstructure, either with or without alendronate pretreatment, and furthermore examined the correlations between bone markers and microstructure in patients pretreated with alendronate as a means to predict patient response to treatment. Among different markers indicative of BMD changes, PINP reflecting collagen formation, appeared to be the most sensitive. In a *post hoc* analysis of changes in bone markers and three-dimensional indices of bone microstructure in paired iliac crest biopsies from a prospective teriparatide treatment study in postmenopausal women with osteoporosis who were either treatment-naive (TN, n = 16) or alendronate-pretreated (ALN, n = 29) at teriparatide initiation. Teriparatide (20 µg/day) was given for 24 months; biopsies were taken at baseline and endpoint, and serum concentrations of PINP and type 1 collagen cross-linked C-telopeptide (CTX) were measured at intervals up to 24 months. In the TN and ALN groups, respectively, mean (SD) increases in three-dimensional bone volume/tissue volume were 105% (356%, $p = 0.039$) and 55% (139%, $p < 0.005$) and trabecular thickness 30.4% (30%, $p < 0.001$) and 30.8% (53%, $p < 0.001$). No significant changes were observed in trabecular number or separation. In the ALN patients, 3-month change of neither PINP nor CTX correlated with indices of cancellous bone microstructure. However, 12-month changes in biochemical bone markers correlated significantly with improvements in bone volume/tissue volume, $r = 0.502$ ($p < 0.01$) and r =

0.378 ($p < 0.05$), trabecular number, $r = 0.559$ ($p < 0.01$) and $r = 0.515$ ($p < 0.01$), and reduction of trabecular separation, $r = -0.432$ ($p < 0.05$) and $r = -0.530$ ($p < 0.01$), for PINP and CTX, respectively. The present analysis showed that cancellous bone microstructure is significantly improved with teriparatide treatment, whether or not patients receive antiresorptive pretreatment (24).

Drake et al. (2011) examined effects of intermittent parathyroid hormone treatment (teriparatide, 40 µg/day) on gene expression in osteoprogenitor cells derived from postmenopausal women (n = 20). Haematopoietic osteoprogenitor cells were isolated from bone marrow samples using magnetic activated cell sorting. Serum PINP and CTX increased in teriparatide-treated subjects (by 97% and 30%, respectively, $p < 0.001$). Bone marrow lineage negative /alkaline phosphatase positive from teriparatide-treated subjects showed an increase in the RANKL / osteoprotegerin (OPG) mRNA ratio (by 7.5-fold, $p = 0.011$) and in the mRNAs for c-fos (a known PTH-responsive gene, by 42%, $p = 0.035$) and vascular endothelial growth factor (VEGF)-C ligand (by 57%, $p = 0.046$). Even short term (14 days) teriparatide treatment resulted in a robust increase in markers of bone formation. Increased VEGF-C production by bone marrow osteoprogenitor cells may promote angiogenesis and the anabolic response to teriparatide. Treatment furthermore resulted in a significant decrease in a panel of bone morphogenetic protein (BMP) target genes. While this observation is not consistent with the anabolic effects of teriparatide on bone and requires further validation, the authors suggested that inhibition of BMP signalling by teriparatide may, over time, limit the availability of mature osteoblasts on bone surfaces and thereby contribute to the observed attenuation of the anabolic response to teriparatide (20).

Kleerekoper et al. (2014) aimed to assess effects of teriparatide treatment on BMD, bone microarchitecture and bone strength. Data from 30 postmenopausal women with severe osteoporosis were analysed in phase-4, open-label study treated with 20 µg teriparatide per day over 18 months. Standard DXA technology and high-resolution magnetic resonance imaging (MRI) and finite element analysis of QCT scans were used for bone analysis. No significant changes were observed for the primary outcome, i.e. surface-to-curve ratio of the distal aspect of the radius from baseline to month 18, as determined by high-resolution MRI. A possible explanation is that teriparatide treatment increases cortical remodelling, resulting in transient 'cortical porosity' and an apparent loss of areal BMD as measured by DXA. The secondary outcomes, i.e. areal BMD, volumetric BMD, finite element analysis estimates of vertebral and hip strength, and bone turnover markers, were consistent with the known osteo-anabolic effect of teriparatide: At month 18, the least-squares mean percentage change from baseline in total volumetric BMD at the spine was 10.05% (95% confidence interval [CI]: 6.83%, 13.26%; $p < 0.001$), and estimated spine strength increased 17.43% (95% CI: 12.09%, 22.76%; $p < 0.001$). Total volumetric BMD at the hip increased 2.22% (95% CI: 0.37%, 4.06%; $p = 0.021$) and estimated hip strength increased 2.54% (95% CI: 0.06%, 5.01%; $p = 0.045$). Areal BMD increased at the lumbar spine and femoral neck, was unchanged for the total hip and at the distalmost aspect of the radius, and decreased at a point one-third of the distance between the wrist and elbow. Bone turnover markers (i.e. P1NP and CTX) increased at months three, six and twenty-four (all $p < 0.05$). No unexpected adverse events were observed. These findings and increases in bone turnover markers are consistent with and confirm the osteoanabolic effect of teriparatide (46).

Experimental studies demonstrated that PTH exposure increases the secretion of periostin, a protein involved in the collagen cross-link formation but the effect of teriparatide treatment on periostin is not currently known. In a two-year open-label single-arm study, Gossiel et al. (2018)

enrolled 20 women with postmenopausal osteoporosis. Teriparatide (20 µg s.c. daily) was administered over 104 weeks. Periostin and sclerostin as well as Dickkopf-related protein1 (DKK-1, a Wnt signalling inhibitor), PINP and CTX were measured in fasting serum collected at baseline (two visits) then at weeks 1, 2, 4, 12, 26, 52, 78 and 104. Bone mineral density was measured at the lumbar spine, total hip and femoral neck. Periostin levels increased by 6.6% (95% CI: -0.4, 13.5) after 26 weeks teriparatide treatment and significantly by 12.5% (95% CI: 3.3, 21.0, $p < 0.01$) after 52 weeks. Change in periostin was positively correlated with change in lumbar spine BMD at week 52 ($r = 0.567$; 95% CI: 0.137, 0.817; $p < 0.05$) and femoral neck BMD at week 104 ($r = 0.682$; 95% CI: 0.261, 0.885; $p < 0.01$). Substantial increases in circulating levels of the Wnt inhibitors sclerostin and DKK-1 were also observed. Similar, PINP and CTX increased significantly during teriparatide treatment, with peaks at week 52 by 204% (95% CI: 119%, 289%) and 227% (95% CI: 116%, 338%), respectively ($p < 0.001$). The authors stated that the observed increase in the bone formation markers may be related to the increase in the rate of bone remodelling but additional studies are needed for verification (32).

The skeletal histomorphometry in patients on teriparatide or zoledronic acid therapy (SHOTZ) study assessed the progressive effects of 2 years of treatment with teriparatide and zoledronic acid on bone remodelling and material properties in postmenopausal women with osteoporosis. Biochemical and histomorphometric bone formation indices were significantly higher in patients receiving teriparatide versus zoledronic acid. The study comprised a 12-month primary study period, with treatment (teriparatide 20 µg/day, s.c. or zoledronic acid 5 mg/year by i.v. infusion) randomised and double-blind until the biopsy at month 6 (teriparatide, $n = 28$; zoledronic acid, $n = 30$ evaluable), then open-label, with an optional 12-month extension receiving the original treatment. A second biopsy (teriparatide, $n = 10$; zoledronic acid, $n = 9$) was collected from the contralateral side at month 24. Findings confirmed that both teriparatide and zoledronic acid increase clinical measures of BMD and reduce fracture risk but underlying mechanism for the BMD increase with each drug is different, as discernible via bone mineralisation density distribution (BMDD) results: Whereas teriparatide stimulated new bone formation, producing a bone matrix mineralisation that remained relatively heterogeneous with a stable mean mineral content with continuation of therapy, treatment with zoledronic acid slowed the bone turnover rate, which would prolong secondary mineralisation, producing a more homogeneous and, over time, a more highly mineralised bone matrix (16, 17).

Effects on vitamin D

Since PTH increases the conversion of 25-hydroxyvitamin D [25(OH)D] to 1,25 dihydroxyvitamin D [$1,25(OH)_2D$], Cosman et al. (2012) assessed the changes in serum concentration of vitamin D metabolites during teriparatide therapy (20 µg/day, s.c.) in the double-blind Fracture Prevention Trial of postmenopausal women with osteoporosis and in the study of men with osteoporosis (see also section 2.5.4.2). Patients were randomised to teriparatide or placebo and received daily supplements of calcium 1000 mg and vitamin D 400 - 1200 IU. Serum concentrations of $1,25(OH)_2D$ and 25(OH)D were measured. In women ($n = 336$), median $1,25(OH)_2D$ concentrations at one month increased from baseline by 27% ($p < 0.0001$) in the teriparatide group versus -3% ($p = 0.87$) in the placebo group (between group $p < 0.0001$). At 12 months, the increase was 19% ($p < 0.0001$) in the teriparatide group versus -2% ($p = 0.23$) in the placebo group ($p < 0.0001$). Median 25(OH)D concentrations after 12 months decreased by 19% ($p < 0.0001$) in the teriparatide group versus 0% ($p = 0.13$) in the placebo group ($p < 0.0001$). Similar observations were made in men. Therefore, treatment with teriparatide increases $1,25(OH)_2D$ concentrations and decreases 25(OH)D concentrations. This

effect may contribute to the biological effects of teriparatide, for example, to stabilise calcium balance by increasing intestinal calcium absorption and renal calcium conservation (12).

In summary, with intermittent administration, teriparatide appears to contain all the anabolic properties of the full-length PTH. The peptide stimulates osteoblastic bone formation and increases remodelling, thereby improving bone quality and bone mass. Both experimental and clinical studies have shown a rise in biochemical markers of bone formation (e.g. PINP as reference marker) during the first months of teriparatide treatment without an accompanying increase in bone resorption. At least in the early stages of administration, bone formation exceeds bone resorption. Dynamic bone histomorphometry parameters such as percent of mineralisation surface / bone surface correlate with serum PINP during teriparatide treatment. A continuous effect on trabecular and cortical bone results in enhanced BMD values and a decreased risk of fragility fractures. The currently available data indicate that the beneficial activity of teriparatide is fully exploited by therapy duration of 24 months.

2.5.4 Overview of efficacy

2.5.4.1 Relationship between efficacy, dose, dosage regimen and administration route

<u>*Evaluation of daily doses*</u>
In an early dose-response study, 51 postmenopausal women with osteoporosis were enrolled in a double-blind, multicentre, placebo-controlled study. The primary objective of the study was to establish a range of safe and potentially effective doses of teriparatide in the treatment of postmenopausal osteoporosis. The primary endpoint for the efficacy evaluation was to characterise the dose dependent effect of teriparatide based on biochemical markers of bone formation (PCIP and serum bone specific alkaline phosphatase [BSAP]) and resorption (urine amino-terminal cross-linked telopeptide of type 1 collagen [NTX]). A safety analysis of data was performed including discontinuation percentage and incidence of adverse events by dose. The planned duration of the treatment phase and follow-up phase was both 6 weeks. The patients were randomised to receive either teriparatide 6 µg/day (n = 4), teriparatide 15 µg/day (n = 8), teriparatide 30 µg/day (n = 9), teriparatide 40 µg/day (n = 6), teriparatide 50 µg/day (n = 8), teriparatide 60 µg/day (n = 7) or placebo (n = 9). A response for the markers of bone formation serum PICP and BSAP between 15- and 40 µg/day doses could be observed. Statistically significant differences from baseline were observed in both PICP and BSAP with doses as low as 15 µg/day, and 6 µg/day appeared to be a no-effect dose. There was an increase in the incidence of adverse events on doses above 40 µg/day. Findings from this and additional dose-response analyses indicated the 20-µg/day dose as superior regarding combined assessment of efficacy and tolerability (G2).

<u>*Morning versus evening dose*</u>
Michalska et al. (2012) examined the long-term effects (12-month treatment) of the morning versus the evening teriparatide (20 µg, s.c.) on BMD and bone turnover markers in an open-label study. Fifty women with established postmenopausal osteoporosis were randomised to administration in the morning or in the evening. The BMD and serum concentrations of CTX and PINP, and tartrate-resistant acid phosphatase isoform 5b were measured at baseline, after 6 and 12 months. After 12 months, the lumbar spine BMD grew markedly ($p < 0.001$) with a significantly greater increase in the morning arm compared to the evening arm (9.1% vs. 4.8%, respectively, $p < 0.05$). The BMD at the distal radius significantly decreased ($p < 0.001$), with no differences between the groups. The BMD at proximal femur did not change significantly.

After 6 months, the BTMs were significantly increased compared with baseline ($p < 0.001$). The increases in the evening arm vs. the morning arm, however, were more pronounced in PINP and in tartrate-resistant acid phosphatase isoform 5b (both $p < 0.05$). According to the authors, timing of teriparatide administration may affect its efficacy but larger studies are needed for confirmation (59).

Cyclic administration

Cosman et al. (2015) investigated 3-month cyclical teriparatide use in 150 postmenopausal women with osteoporosis either treatment naïve (n = 86) or pretreated with alendronate (n = 64). Within cohorts, women were randomised to daily teriparatide for 24 months or four 3-month teriparatide cycles, each followed by 3 months off (12 months total teriparatide). In treatment naïve women, BMD increased in the lumbar spine, total hip, trochanter and femoral neck in daily and cyclic groups (within groups, $p < 0.0002$, except cyclic femoral neck, $p = 0.13$). Increases were 2-fold greater in daily vs. cyclic groups (all sites $p < 0.05$). In daily vs. cyclic groups, radius BMD declined (-4.2 vs. -2.1%, respectively; both $p < 0.01$; group difference, $p = 0.08$) and total bone mineral increased modestly (1.4%, $p = 0.18$; vs. 1.5%, $p = 0.06$; group difference, not significant). In pretreated women, there were no group differences. The authors stated that cyclic teriparatide over 2 years improved BMD similarly to daily treatment in women who remained on alendronate, despite only 50% of the teriparatide dose. However, there does not appear to be a BMD advantage to cyclic administration in treatment-naive women for up to 24 months (13).

Treatment duration

Based on the potential risk of osteosarcoma (for details see section 2.5.5.2), teriparatide therapy is limited to 24 months and a treatment course should not be repeated over a patient's lifetime. However, there is some uncertainty about how long patients should be treated to achieve the best outcomes. Lindsay et al. (2016) reviewed the published information regarding continuous therapy. Most data on bone turnover markers is available over first year of therapy, but some studies measured biochemical markers during a full 24-month treatment course. There is one study of patients with glucocorticoid-induced osteoporosis (GIO) examining teriparatide versus alendronate where the increases in biochemical markers of bone formation exceeded those of resorption over the 36-month treatment period. In this study, GIO patients treated with teriparatide for 36 months had greater increases in BMD and fewer new vertebral fractures than subjects treated with alendronate (78). According to Lindsay et al., there is evidence that the increase in bone formation markers PINP and osteocalcin exceeded the increase in CTX throughout the 24-month treatment course, although all markers peak between 6 and 12 months of therapy. an explanation of these observation may be that teriparatide results in overfilling of resorption sites, then ongoing teriparatide treatment, even in the setting of high levels of bone resorption, will result not only in replacement of old bone with a similar amount of new healthy bone but will result in ongoing anabolism. This hypothesis is strengthened by clinical trials repeatedly demonstrating that teriparatide's reduction of the fracture risk appears to increase with longer duration of therapy despite a trend of markers returning to baseline (Figure 5). The authors conclude that for patients with osteoporosis at high risk for fracture treated with teriparatide, available information suggests that the full 24-month treatment course is important to achieve the best clinical outcomes (52).

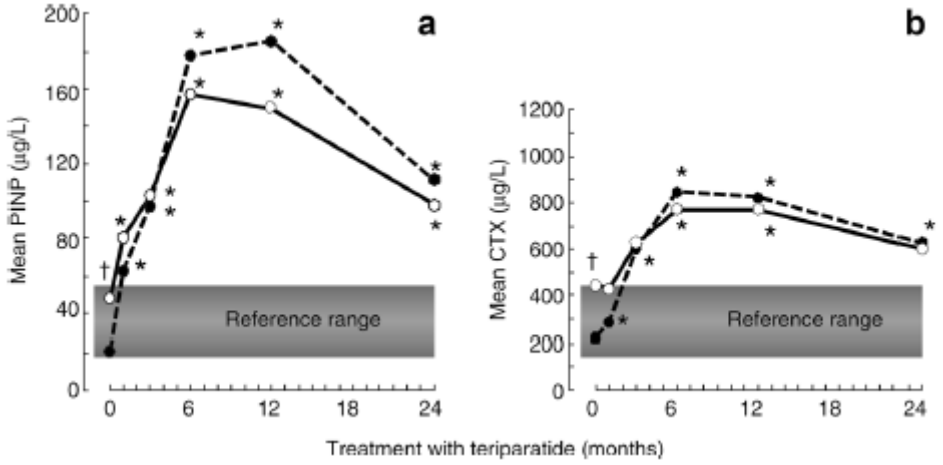

Figure 5: Changes in biochemical markers of bone turnover (PINP and CTX) in patients treated with teriparatide. Solid lines indicate treatment-naïve patients (n = 16), and dotted lines indicate alendronate-pretreated patients (n = 29) (52)
*p < 0.05 versus from baseline, †p < 0.05 between groups

Immunogenicity
The stimulation of bone turnover by teriparatide is known to subside slowly after 12 months of administration (as displayed in Figure 5) and a response to a second course of therapy appears to be diminished. There is currently no evidence that these observations are related to the development of blocking antibodies. In the Fracture Prevention Trial, circulating antibodies to teriparatide were documented in one woman in the placebo group (< 1%), 15 women in the 20-µg group (3%), and 44 in the 40-µg group (8%), but these antibodies had no discernible effects on any of the other measurements (65). Currently, there are no data indicating that antibodies adversely affect the efficacy of teriparatide when the agent is used as recommended (28).

Based on the experience with different doses and treatment durations, the recommended posology is intermittent treatment, i.e. daily s.c. administration of a 20 µg-dose of teriparatide over 24 months (G1).

2.5.4.2 Clinical trial efficacy data

Fracture Prevention Trial
Neer et al. (2001) published findings from the Fracture Prevention Trial that enrolled 1637 postmenopausal women with prior vertebral fractures to randomly receive 20 µg (n = 541) or 40 µg (n = 552) teriparatide or placebo (n = 544), daily administered s.c. by the women themselves (?). Calcium (1000 mg) and vitamin D (400 - 1200 IU) supplements were used daily. Vertebral radiographs were obtained at baseline and at the end of the study (median duration of observation: 21 months) and serial measurements of bone mass performed by DXA. New vertebral fractures occurred in 14% of the women in the placebo group and in 5% and 4%, respectively, of the women in the 20 µg and 40 µg active treatment groups; the respective relative risks (RR) of fracture in the 20 µg and 40 µg groups, as compared with the placebo group, were 0.35 and 0.31 (95% CI: 0.22, 0.55 and 0.19, 0.50). New non-vertebral fragility fractures occurred in 6% of the women in the placebo group and in 3% of those in each teriparatide group (RR: 0.47 and 0.46, respectively [95% CI: 0.25, 0.88 and 0.25, 0.861, see also Figures 6 and 7). As compared with placebo, the 20-µg and 40-µg doses of teriparatide

increased BMD by 9% and 13% in the lumbar spine and by 3% and 6% in the femoral neck; the 40-µg dose decreased BMD at the shaft of the radius by 2%. Both doses increased total-body bone mineral by 2 to 4%. The authors concluded that teriparatide decreases the risk of vertebral and non-vertebral fractures. The drug increases vertebral, femoral and total-body BMD, and is well tolerated (65).

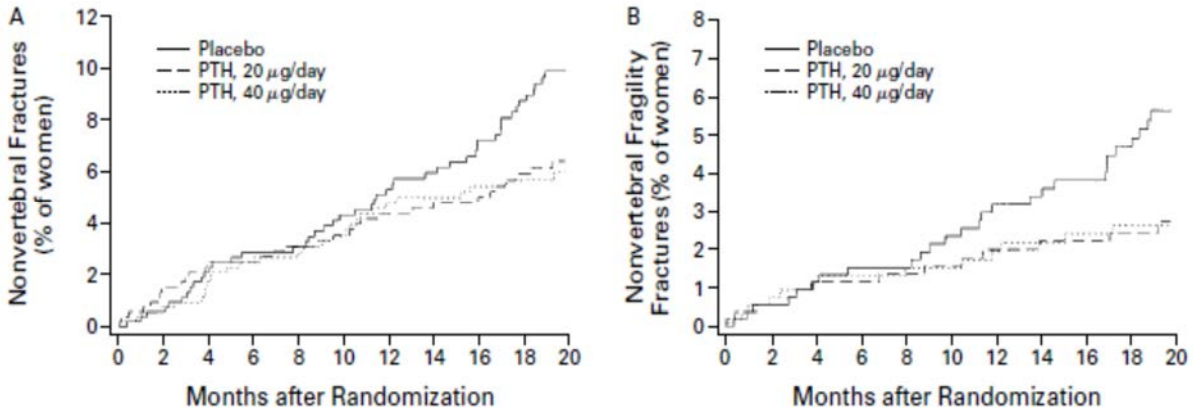

Figure 6: Cumulative proportion of women assigned to placebo or active treatment (20 µg or 40 µg teriparatide [PTH]) who had one or more non-vertebral fractures (panel A) and the cumulative proportion who had one or more non-vertebral fragility fractures (panel B) in the Fracture Prevention Trial (65)

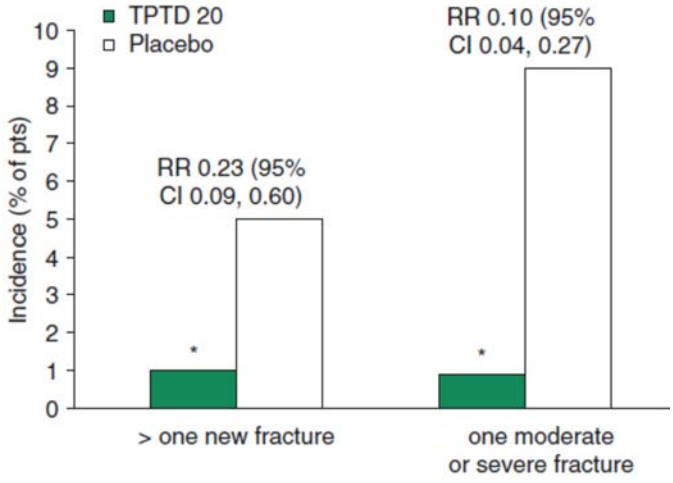

Figure 7: Efficacy of teriparatide in preventing new vertebral fractures in patients (pts) with postmenopausal osteoporosis in the Fracture Prevention Trial. Bars reflect the incidence of new multiple or moderate or severe vertebral fractures after a median 21 months of treatment with teriparatide (TPTD) 20 µg/day or placebo (PL) in ambulatory women (n = 1637) (4, 65)
RR- relative risk, CI - confidence interval; * $p \leq 0.001$

EFOS and ExFOS data

The European Forsteo Observational Study (EFOS) was a 36-month, prospective, observational study designed to evaluate fracture outcomes, back pain and HRQoL in postmenopausal women with severe osteoporosis treated with teriparatide in the outpatient setting for a maximum of 18 months, followed by a post-teriparatide treatment period of a further 18 months. The incidence

of clinical vertebral and non-vertebral fragility fractures, back pain, and health-related quality of life (HRQoL, EQ-5D [mobility, self-care, usual activities, pain and discomfort as well as anxiety and depression]) were assessed. Spontaneous reports of adverse events were collected. All 1648 enrolled women were teriparatide treatment-naive, 91.0% of them had previously received other anti-osteoporosis drugs, and 72.8% completed the 18-month study. A total of 168 incident clinical fractures were sustained by 138 (8.8%) women (821 fractures / 10,000 patient-years). A 47% decrease in the odds of fracture in the last 6-month period compared to the first 6-month period was observed ($p < 0.005$). Mean back pain VAS (visual analogue scale) was reduced by 25.8 mm at endpoint ($p < 0.001$). Mean change from baseline in overall health status using the EQ-VAS was 13 mm by 18 months. The largest improvements were reported in the EQ-5D subdomains of usual activities and pain / discomfort (48).

In 2011, Fahrleitner-Pammer et al. reported the main study analyses for the total study cohort followed up for 36 months, i.e., the incidence of clinical vertebral and non-vertebral fractures and changes in back pain, both during teriparatide treatment and in the 18 months after teriparatide discontinuation. A total of 208 (13.2%) of 1576 patients sustained 258 fractures during 36 months of follow-up: 34% were clinical vertebral fractures and 66% non-vertebral fractures. The adjusted odds of fracture were reduced during teriparatide treatment and there was no evidence of further change in the 18-month post-teriparatide period, during which 63.3% patients took bisphosphonates. A 74% decrease in the adjusted odds of fracture in the 30- to < 36-month period compared with the first 6-month period was observed ($p < 0.001$). Back pain decreased during teriparatide treatment and this decrease was sustained after teriparatide discontinuation (Figure 8). Adjusted mean back pain VAS decreased by 26.3 mm after 36 months ($p < 0.001$) from baseline mean of 57.8 mm. The authors concluded that in a real-life clinical setting, the risk of fracture decreased during teriparatide treatment, with no evidence of further change after teriparatide was discontinued. The changes in back pain seen during treatment were maintained for at least 18 months after teriparatide discontinuation. While the results should be interpreted in the context of the design of an observational study, the authors emphasised that was no evidence of deterioration in the odds of fracture or a rebound increase in back pain after teriparatide was discontinued (25).

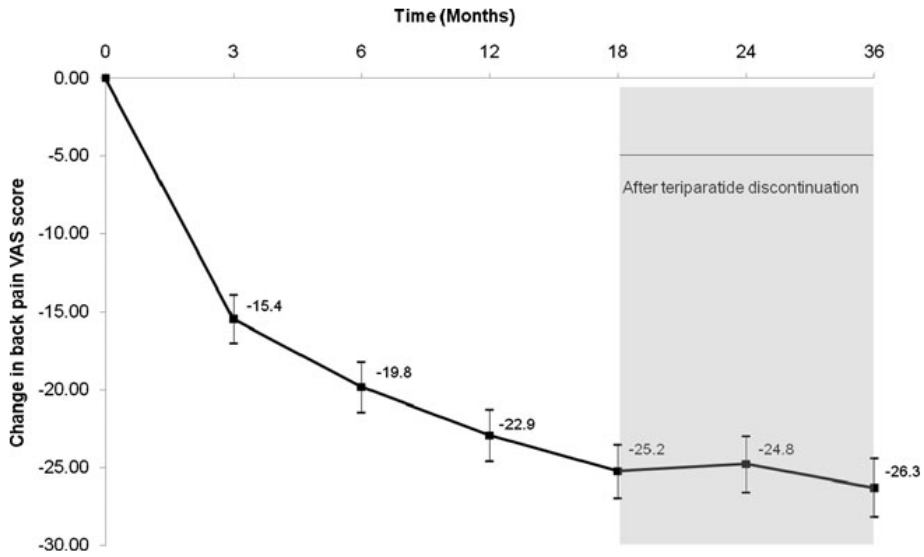

Figure 8: Back pain VAS: adjusted mean change (95% CI) from baseline during and after teriparatide treatment in the total EFOS study cohort (25)

Further analyses on the EFOS study data were performed by Jakob et al. (2012) and Ljunggren et al. (2013). Of the 1581 patients completing 18 months of treatment, 48.4% had a recent prior fracture and 15.6% of these patients had an incident fracture during follow-up; furthermore, 10.9% of the 816 patients with no recent prior fracture had an incident fracture. Quality of life (EQ-VAS and EQ-5D index scores) improved significantly from baseline to 18 months and this improvement was maintained over the 18-month post-teriparatide period. Improvements were seen across all five EQ-5D domains during teriparatide treatment that were maintained after teriparatide was discontinued. Subjects with incident clinical fractures had significantly less improvement in EQ-VAS than those without incident fractures. Recent prior fracture did not influence the change in EQ-VAS during treatment (39, 54). Walsh et al. (2012) performed a subgroup analysis of 589 postmenopausal women with osteoporosis aged ≥ 75 years. During the 36-month observation period, 87 (14.8%) women sustained a total of 111 new fractures: 37 (33.3%) vertebral fractures and 74 (66.7%) non-vertebral fractures. Adjusted odds of fracture were decreased by 80% in the 30 to < 36-month interval compared with the first 6-month interval ($p < 0.009$). Although the older subgroup had higher back pain scores and poorer HRQoL at baseline than the younger subgroup, both age groups showed significant reductions in back pain and improvements in HRQoL post baseline. In conclusion, patients ≥ 75 year and < 75 years benefited to a similar extent (89).

The Extended Forsteo Observational Study (ExFOS) was a non-interventional, prospective, single-cohort, observational study conducted in eight European countries. It addressed the need for a large real-life clinical practice study of teriparatide treatment after the update of the teriparatide European label, i.e. the consistent treatment duration of 24 months, as well as the newly approved therapeutic indications (i.e. GIO) in the context of osteoporosis treatment guidelines in the participant countries. Napoli et al. (2018) reported the incidence of clinical vertebral and non-vertebral fractures, as well as changes in back pain and HRQoL over 42 months (i.e. up to 24 months of teriparatide treatment and 18 months of follow-up after stopping teriparatide). Of 1531 patients analysed (90.7% female, mean age: 70.3 years), 76 (5.0%) never took teriparatide. For the remaining patients , median treatment duration was 23.6 months. The adjusted odds of clinical fracture decreased by 47% in the > 12- to 18-month treatment period ($p = 0.013$) compared with the first 6-month period, with no statistically significant reduction in the > 18- to 24-month interval. The clinical fracture rate remained stable during the 18 months post-teriparatide, when approximately 98% of patients took osteoporosis medication (51% bisphosphonates). Clinical vertebral fractures were reduced at every time period compared with the first 6 months. Adjusted mean back pain scores decreased and EQ-5D scores increased significantly at each post-baseline observation. This study confirmed observations from the earlier EFOS study: In a real-life clinical setting, the risk of clinical fractures declined during 24 months of teriparatide treatment. This reduction was maintained 18 months after stopping teriparatide (64).

Maugeri et al. (2009) described experiences in using teriparatide for the treatment of severe osteoporosis in a sample of 141 elderly women of mean age 73.4 ± 5.8 years, with a mean number of fractures of 3.0 ± 0.85, with a spine deformity index of 5.92 ± 1.27 and a mean vertebral T-Score (L1-L4) of -3.15 ± 0.39 and a mean femoral T-Score of -2.50 ± 0.28. All patients had been treated with antiresorptive drugs for at least one year, specifically, 70 with alendronate, 42 with risedronate and 29 with raloxifene. For 18 months, all these patients were injected subcutaneously with 20 µg of teriparatide, with the daily addition of 1 g of calcium and 880 IU of vitamin D. The study was continued for 24 months, at the end of which the patients continued to take only calcium and vitamin D. The patients underwent BMD analysis of the vertebral column and femur every 6 months. The Quality-of-Life Questionnaire of the European

Foundation for Osteoporosis (QUALEFFO, 41 items) questionnaire was used to evaluate the changes in the quality of life (QoL) and the consumption of non-steroidal anti-inflammatory drugs (NSAIDs) was also recorded. The results showed that teriparatide protected 96.5% against new fractures (only five new fractures occurred), BMD increased approximately by 12% in the vertebral column and by 11% in the femur, consumption of NSAIDs was reduced at an early stage approx. 80%, QoL improved considerably and remained so during the 18 months of teriparatide treatment, with only a slight decrease during the 6 subsequent months (58).

Oswald et al (2014) reported an observational study involving patients (n = 323) with severe spinal osteoporosis (bone density T-score of ≤ -4) who were treated at a specialist osteoporosis clinic with teriparatide (20 µg for 24 months; n = 217) or standard care (n = 106) over a 5.5-year period. The standard care group did not receive teriparatide because they declined to self-inject (59.4%), had a contraindication (7.5%) or were already stabilised on oral bisphosphonates (33%). The two groups were matched for the severity of osteoporosis, fracture risk and most other clinical variables. The annual percentage change in lumbar spine BMD was greater in the teriparatide group (8.2 ± 6.0 vs. 5.0 ± 8.4, p = 0.002), but there was no difference in response of hip BMD. During follow-up, 3/217 (1.4%) teriparatide-treated patients had new vertebral fractures compared with 7/106 (6.6%) receiving standard care (p = 0.011), but there was no difference between the groups in the rate of non-vertebral fractures (11.1 vs. 8.5%, p = 0.47). Logistic regression analysis adjusting for baseline characteristics showed that the risk of vertebral fractures in teriparatide-treated patients was significantly reduced compared with standard care (odds ratio [OR]: 0.12, 95% CI: 0.03, 0.55, p = 0.007). The authors stated that teriparatide may be the preferred treatment in patients with severe spinal osteoporosis (71).

In a retrospective survey of 48 women (mean age 73.2 years) with severe osteoporosis and prevalent fractures, Mok et al. (2018) aimed to determine time-dependent changes in BMD at skeletal sites in association with teriparatide therapy. BMD was measured at baseline, 6 - 12 months and 18 - 24 months at the lumbar spine, total hip and femoral neck. Bone turnover markers were determined at 3 - 12 and 12 - 24 months. BMD increased at 6 - 12 months (% change mean [SEM] 6.5 [1.1]; p = 0.004) and 18 - 24 months (8.45 % [1.2]; p < 0.001) at the lumbar spine. A significant increase in BMD was observed at femoral neck (3.1% [1.3%]; p = 0.02). Changes in BMD at the total hip was higher in patients younger than 73 years compared to older women (% change in BMD 4.13% [1.64%] vs. -1.7 [1.1]; p = 0.007). The authors concluded, although further larger confirmatory studies are needed, that in patients with severe osteoporosis age may influence the skeletal response to teriparatide in the real-life setting (63).

Focus on osteoporosis in men

In a study performed by Orwoll et al. (2003), 437 men with spine or hip BMD density more than 2 SD below the young adult male mean were randomised to daily s.c. injections of placebo, teriparatide 20 µg or teriparatide 40 µg. All subjects also received supplemental calcium and vitamin D. The study was stopped after a median duration of 11 months because of a finding of osteosarcomas in rats in routine toxicology studies. Biochemical markers of bone formation increased early in the course of therapy and were followed by increases in indices of osteoclastic activity. Spine BMD was greater than in placebo subjects after 3 months of teriparatide therapy, and by the end of therapy it was increased by 5.9% (20 µg) and 9.0% (40 µg) above baseline (p < 0.001 vs. placebo for both comparisons). Femoral neck BMD increased 1.5% (20 µg; p = 0.029) and 2.9% (40 µg; p < 0.001), and whole body bone mineral content increased 0.6% (20 µg; p = 0.021) and 0.9% (40 µg; p = 0.005) above baseline in the teriparatide subjects. There was no change in radial BMD in the teriparatide groups. BMD responses to teriparatide were

similar regardless of gonadal status, age, baseline BMD, BMI, smoking or alcohol intake. Subjects experienced expected changes in mineral metabolism. Adverse events were similar in the placebo and 20-µg groups, but more frequent in the 40- µg group. According to the authors, these results underline that teriparatide presents a useful therapy for osteoporosis in men (70).

Niimi et al. (2015) retrospectively compared the effects of daily teriparatide therapy (20 µg) in men (n = 75) and postmenopausal women (n = 488) with osteoporosis and investigated biochemical markers of bone turnover to detect possible sex differences. The primary efficacy measures were changes in lumbar spine and femoral neck BMD after 12 months of treatment. Changes in serum levels of PINP and urinary NTX excretion after 4, 8 and 12 months of treatment were also measured. In men, lumbar spine BMD significantly increased by 11.3 ± 9.9% and femoral neck BMD increased by 0.4 ± 6.4%. In postmenopausal women, lumbar spine BMD significantly increased by 9.6 ± 8.1% and femoral neck BMD increased by 2.4 ± 7.8%. The absolute increases in PINP were similar in both groups at 4, 8 and 12 months but the absolute increases in urinary NTX were lower in men than in women at 8 and 12 months. The authors concluded that daily teriparatide treatment was as effective in men as in postmenopausal women regardless of sex differences (66).

Pivotal placebo-controlled trials as well as observational studies with treatment periods between 18 and 24 months reported an increase in BMD (demonstrated by non-invasive imaging methods) and a reduction in the risks of vertebral and non-vertebral fractures both in women and men suffering from osteoporosis. An accompanying beneficial effect on back pain was also observed.

2.5.4.3 Effect of prior therapy

The European Study of Forsteo (EUROFORS) was a 2-year, prospective, randomized trial of postmenopausal women with established osteoporosis designed to investigate various sequential treatment regimens (including teriparatide) after one year of teriparatide therapy. Obermayer-Pietsch et al. (2008) examined BMD response and safety in a subgroup of 503 women with osteoporosis who received teriparatide for 24 months. Patients were divided into three groups based on their previous antiresorptive treatment: treatment: treatment-naïve (n = 84); pretreated with no evidence of inadequate treatment response (n = 134) and pretreated showing an inadequate response to antiresorptive treatment (n = 285), which was predefined based on the occurrence of fractures, persistent low BMD, and/or significant BMD loss while on therapy. Changes in BMD from baseline were analysed using mixed model repeated measures. Lumbar spine BMD increased significantly from baseline at 6, 12, 18 and 24 months in all three groups. The mean gain in spine BMD over 24 months was greater in the treatment-naïve group (0.095 g/cm^2; 13.1%) than in the pretreated (0.074 g/cm^2; 10.2%; $p < 0.005$) and inadequate responder (0.071 g/cm^2; 9.8%; $p < 0.001$) groups. The corresponding increases in total hip BMD were 3.8%, 2.3% and 2.3%, respectively. Early decreases in hip BMD in the inadequate responder group were reversed by 18 months of treatment. Increases in BMD between 18 and 24 months were highly significant. Whereas teriparatide treatment for 24 months was associated with a significant increase in BMD in patients with and without previous use of antiresorptive treatment, pretreatment modestly attenuated the BMD response to teriparatide. Safety was consistent with current prescribing label information (69).

In the framework of EUROFORS, Blumsohn et al. (2011) examined biochemical markers of bone formation in women with osteoporosis treated with teriparatide and determined: (1) whether the response is associated with prior osteoporosis therapy, (2) which marker shows the best performance for detecting a response to therapy, and (3) the correlations between early changes in bone markers and subsequent BMD changes after 24 months of teriparatide. The bone turnover markers PINP, bone-specific alkaline phosphatase (ALP) and total ALP were measured at baseline, 1 and 6 months, and change in BMD at the lumbar spine, total hip and femoral neck from baseline to 24 months. A total of 758 postmenopausal women with established osteoporosis (n = 181 treatment-naïve) were included in the analysis. Significant increases in formation markers occurred after one month of teriparatide regardless of prior osteoporosis therapy. The absolute increase at one month was lower in previously treated versus treatment-naïve patients, but after 6 months all groups reached similar levels. PINP showed the best signal-to-noise ratio. Baseline PINP correlated positively and significantly with BMD response at 24 months. The authors stated that the long-term responsiveness of bone formation markers to teriparatide is not affected in subjects previously treated with antiresorptive drugs (5).

These findings were confirmed by Hofstetter et al. (2014) who examined effects of 2 years of teriparatide treatment on mineral and organic matrix properties of the newest formed bone in patients who were previously treatment-naïve (n = 16) or on long-term alendronate therapy (n = 24). The analysis of biopsies suggested that prior alendronate use does not blunt the favourable effects of teriparatide on bone quality (37).

Non-responders
A retrospective chart review of 78 patients with osteoporosis who completed 18 - 24 months of teriparatide therapy aimed to identify factors associated with none or insufficient treatment response. The overall group showed a 10.7% increase in lumbar spine BMD after 24 months of treatment. Eighty-three percent were considered responders defined as ≥ 3.0% increase in lumbar spine BMD. However, 16.7% were assessed as non-responders (mean change of lumbar spine BMD: -1.4%). No difference in previous bisphosphonate use or in baseline vitamin D, calcium, creatinine, BMI, age, gender or prior fracture history was observed between responders and non-responders. No consistent pattern of change in measures of bone markers was noted between responders and non-responders. According to the authors, teriparatide combination therapy with denosumab or zoledronic acid may pose an option in these patients, but additional studies dedicated to identifying teriparatide non-responders are warranted (45).

The available data indicate that the majority of osteoporotic patients adequately respond to teriparatide therapy with increases in BMD. None or insufficient response is observed in a minority of patients; reasons for non-responding are currently unknown. Overall, previous bisphosphonate therapy does not attenuate the effect of teriparatide.

2.5.4.4 Comparison studies

Teriparatide versus bisphosphonates
Caggiari et al. (2016) compared the efficacy and tolerability of teriparatide and alendronate in patients with postmenopausal osteoporosis at high risk of fracture in a double-blinded clinical trial. Safety and effectiveness analyses were based on data from 355 women with a mean age of 68 years. Two groups (A and B) with BMD T-score ≤ -2.5 and 3 or more vertebral fractures on radiograph were analysed. Group A: was treated with teriparatide 20 µg/day and composed

from 182 women, in post-menopausal age, without a history of cancer. Group B: was treated with alendronate 10 mg/day composed from 173 women, postmenopausal age, with previous history of cancer (non-active during the study). Clinical evaluations included measuring of bone turnover markers (ALP, PINP and NTX), BMD via DAX and health-related quality of life (HrQoL). Both active treatments were comparable regarding efficacy parameters. Overall tolerability and HrQoL favoured teriparatide in the treatment of patients with osteoporosis at high risk of fracture (9).

The 2-year, randomised, double-blind, active-controlled fracture endpoint VERO ('VERtebral fracture treatment comparisons in Osteoporotic women') study included postmenopausal women with established osteoporosis, who had at least two moderate or one severe baseline vertebral fractures and BMD T-score ≤ -1.5. A total of 1360 women (mean age 72.1 years) were randomised (680 per group). Patients were treated with either s.c. daily teriparatide 20 µg or oral weekly risedronate 35 mg. At 24 months, new vertebral fractures occurred in 28 (5.4%) patients in the teriparatide group and 64 (12.0%) in the risedronate group (risk ratio [RR]: 0.44, 95% CI: 0.29, 0.68; $p < 0.0001$). The risk of new vertebral fractures and clinical fractures (a composite of clinical vertebral fractures and non-vertebral fragility fractures) was reduced by 56% and 52%, respectively, with teriparatide compared with risedronate. In subgroup analyses including previous fracture types, use of glucocorticoids and prior use of osteoporosis drugs, the risk reduction of teriparatide versus risedronate did not significantly differ (29, 42).

Saag et al. (2016) presented the results of a randomised, double-blind, double-dummy, active comparator-controlled study consisting of a 1.5-month screening phase, an 18-month primary phase and an 18-month continuation phase comparing teriparatide (s.c., 20 µg/day, n = 214) with alendronate (oral, 10 mg/day, n = 214) for treating GIO (median 7.5 mg/day prednisone equivalent for ≥ 90 days). Increases in BMD from baseline were significantly greater in the teriparatide group than in the alendronate group. At 36 months BMD increases were 11.0% versus 5.3% for lumbar spine, 5.2% versus 2.7% for total hip, and 6.3% versus 3.4% for femoral neck ($p < 0.001$ for all). In teriparatide-treated patients, the trabecular bone score (TBS) was significantly increased at 18 months compared to baseline and by 36 months had increased 3.7% ($p < 0.05$). In alendronate-treated patients, there was no significant change in TBS compared to baseline at any time point. The authors stated that in patients affected by GIO, both alendronate and teriparatide increased lumbar spine BMD. However, as shown in Figure 9, the TBS score significantly increased only with teriparatide (77).

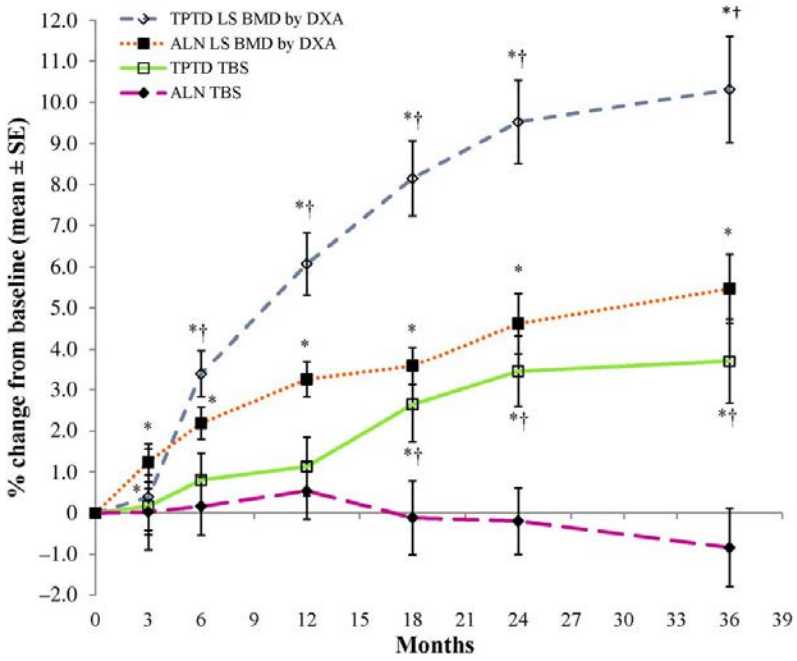

Figure 9: Trabecular bone score (TBS) and bone mineral density (BMD), determined by dual x-ray absorptiometry (DXA) in TBS subpopulation analysis. Values are the mean ± SEM percent change from baseline. *p < 0.05 vs. the same group at baseline; † p < 0.05 for lumbar spine (LS) BMD measured by DXA in teriparatide (TPTD)-treated patients versus LS BMD measured by DXA in alendronate (ALN)-treated patients or for TBS in TPTD-treated patients versus TBS in ALN-treated patients (77)

A total of 92 men (mean age 56.3 years, range: 25 - 82 years) with GIO were included in an 18-month, randomised, open-label trial of teriparatide (20 µg/day, n = 45) and risedronate (35 mg/week, n = 47). Serum biochemical markers of bone formation (i.e. PINP and CTX) were measured at baseline, 3 months, 6 months and 18 months. Both PINP and CTX levels increased in the teriparatide group and decreased in the risedronate group. In addition, teriparatide demonstrated superior efficacy compared to risedronate in the effects on biomechanical indices estimated by high-resolution QCT of the 12th thoracic vertebra (26).

Overall, in studies comparing the efficacy of teriparatide versus bisphosphonate therapy, beneficial effects on BMD and quality of life were more pronounced with the former agent. This was demonstrated in particular in female and male patients affected by glucocorticoid-induced osteoporosis. Effects on the fracture risk were overall comparable.

2.5.4.5 Meta-analyses

Yang et al. (2016) performed a network meta-analysis of pharmacological agents for osteoporosis treatment and fracture prevention. Patients treated by alendronate, denosumab, teriparatide were associated with a reduced risk of new non-vertebral fractures compared to those treated by placebo. Alendronate, denosumab and zoledronic acid had better efficacy in preventing hip fractures. With respect to wrist fractures prevention, no significant difference was observed. The authors employed surface under cumulative ranking curve (SUCRA) to rank probabilities with respect to each clinical outcome. A higher SUCRA value indicates a more

desirable property with respect to a certain endpoint and teriparatide ranked highest in new non-vertebral fractures prevention whereas etidronate and denosumab showed a well-balanced safety and efficacy (91).

A meta-analysis performed by Liu et al. (2017) compared the efficacy and safety of teriparatide versus bisphosphonates in the management of osteoporosis. A total of 1967 patients from eight randomised controlled trials were analysed; outcomes included BMD of the femoral neck, total hip and lumbar spine, vertebral and non-vertebral fractures and any adverse event. A subgroup analysis of treatment effectiveness was performed according to the aetiology of osteoporosis, i.e., GIO versus postmenopausal osteoporosis. Teriparatide increased the BMD of the lumbar spine, femoral neck and total hip to a greater extent than bisphosphonates. Patients treated with teriparatide also had a lower risk of vertebral fractures compared with bisphosphonates; however, no difference in risk of non-vertebral fractures was found. GIO subgroups showed larger increases in BMD of the lumbar spine, total hip and femoral neck in patients treated with teriparatide compared with bisphosphonates. The postmenopausal osteoporosis subgroup showed larger increases in BMD of the lumbar spine in patients treated with teriparatide compared with bisphosphonates. Patients in the GIO subgroup (but not the postmenopausal osteoporosis subgroup) were less likely to suffer a vertebral fracture on teriparatide as compared with bisphosphonates. In contrast, no significant difference in the percentage of non-vertebral fractures was noted between the two types of treatment for either subgroup. This meta-analysis found that teriparatide significantly increased the BMD of lumbar spine, total hip and femoral neck, particularly in GIO-induced osteoporosis, but did not lower the risk of non-vertebral fractures when compared with bisphosphonates (53).

Wang et al. (2017) conducted a comprehensive literature review of PubMED, EMBASE, Cochrane Controlled Trials Registry and the China Academic Journal Network Publishing databases for relevant RCTs of teriparatide versus alendronate in postmenopausal osteoporosis patients. Six trials involving 618 patients were included. The meta-analysis demonstrated a significant increase in lumbar spine BMD (WMD: 3.46, 95% CI: 2.15, 4.77, $p < 0.00001$), but not femoral neck BMD (weighted mean difference [WMD] = 1.50, 95% CI: 0.04, 2.95, $p = 0.04$) in patients treated with teriparatide compared with alendronate for 6 to 18 months. These beneficial effects were apparent in the lumbar spine at 12 months of treatment (WMD: 4.49, 95% CI: 2.57-6.40, $p < 0.01$). Teriparatide was, however, not significantly superior to alendronate in reducing fracture risk (OR: -0.03, 95% CI: -0.12, 0.07; $p = 0.52$) (90).

Meta-analyses confirm the more favourable effect on BMD of teriparatide versus bisphosphonate therapy. Findings regarding the reduction of fracture risk are less consistent; they are pointing to comparable effectivity.

2.5.4.6 Combination therapy

Unlike most common medical conditions, the treatment of osteoporosis is distinctive in that there is no accepted approach for using more than one drug at a time. Over the past decade, however, several studies have explored the skeletal effects of using PTH analogues along with antiresorptive drugs. However, the majority of studies was small, short-term and insufficiently controlled to allow reliable results (51).

Clinical studies combining teriparatide (20 µg daily) plus the SERM raloxifene (60 mg daily) yielded inconsistent results whether concomitant use offers beneficial effects. Similar, available

data from the concurrent use of bisphosphonates and teriparatide do not provide clinical benefits compared to monotherapy, though approaches that involve adding one class of agent to patients already being treated with the other class of agents deserve further exploration. Bone resorption markers were identical in patients treated with denosumab monotherapy and those treated with combined denosumab and teriparatide whereas markers of bone formation were significantly more suppressed in those treated with denosumab alone, especially at the early time points. Overall, findings suggest that the superior efficacy of combined denosumab and teriparatide may be due, at least in part, to denosumab's ability to fully block the pro-resorptive effects of teriparatide while still allowing for teriparatide-induced stimulation of modelling-based bone formation, particularly at anatomic sites rich in cortical bone (51).

At present, a beneficial effect of combination therapy for osteoporosis is unclear.

2.5.4.7 Effects upon retreatment

Finkelstein et al. (2009) investigated the effects of teriparatide retreatment in osteoporotic men and women; subjects previously participated in a 30-month RCT comparing the effects of alendronate (group 1), teriparatide (group 2) or both (group 3) on BMD and bone turnover in men and women with low BMD (phase 1). Subjects who completed phase 1 on their assigned therapy entered phase 2 (months 30 - 42), during which teriparatide was stopped in groups 2 and 3. Teriparatide was administered to all subjects during months 42 to 54 (phase 3). Changes in BMD and markers of bone turnover (serum osteocalcin, P1NP and NTX) between phase 1 and 3 in subjects receiving teriparatide alone were compared. Posterior-anterior and lateral spine BMD increased 12.5 ± 1.5 and 16.9 ± 1.7%, respectively, during the first 12 months of teriparatide administration and 5.2 ± 0.8 and 6.2 ± 1.8%, respectively, during teriparatide retreatment ($p < 0.001$ and $p = 0.001$). Increases in osteocalcin ($p < 0.001$), P1NP ($p < 0.001$) and NTX ($p < 0.001$) were greater during the first period of teriparatide administration. Findings demonstrated that skeletal responses to teriparatide were attenuated when it was re-administered for 12 months after a 12-month hiatus. During the first course of teriparatide therapy, there was a substantial improvement in spine BMD, with most of the increase occurring during the first 12 months of therapy. When teriparatide was re-administered, however, increases in BMD were significantly smaller (28).

It is unknown why the response to a second course of therapy is diminished. The authors discussed several hypotheses: First, development of anti-teriparatide antibodies may offer an explanation but none were detected in the patient collective. Second, the absorption of teriparatide might decrease during long-term therapy but there are no data supporting this theory. Third, prolonged daily teriparatide administration might down-regulate PTH receptors. The acute rise in serum calcium was similar at the beginning and the end of each treatment period, however, arguing against receptor down-regulation. Fourth, it is possible that there is a maximal skeletal response to teriparatide, which was achieved during the initial 2 years of therapy and then reached again during the second course of therapy after a period of bone loss had temporarily reduced bone mass below this theoretical ceiling. The absence of an inverse association between BMD at the start of retreatment and the change in BMD argues against a ceiling effect. Finally, teriparatide target cells, including mature osteoblasts, osteoblast precursors, bone lining cells, or osteoclast precursors, could become depleted during long-term teriparatide therapy leading to a progressive decrease in responsiveness to teriparatide during long-term therapy. If the population of teriparatide target cells were not fully replenished after one year without teriparatide therapy, responsiveness to a repeat course of teriparatide therapy

would also be attenuated (28). Further evaluation is needed when teriparatide is reintroduced after several years. However, while this issue needs further exploration, it is not of imminent relevance since teriparatide is currently authorised for a single 24-month course per lifetime.

There is currently no plausible explanation why the response to teriparatide appears to be attenuated when the drug is reintroduced after effective treatment followed by a 'drug holiday'. While additional exploration is warranted, since the maximum total duration of treatment with teriparatide should not exceed be 24 months, these observations do not affect the current benefit-risk balance of teriparatide.

2.5.4.8 Efficacy in special patient populations

Elderly
Since many individuals are living into their eighth and ninth decades, Niimi et al. (2016) retrospectively compared the usefulness of daily teriparatide therapy in patients with established osteoporosis regarding their age (≥ 80 years and < 80 years) to detect possible age-related differences. The data of 628 patients treated with teriparatide (20 µg/day for 24 months) were analysed. Changes in serum levels of PINP and urinary NTX excretion were also measured. In the older subgroup, lumbar spine BMD significantly increased by 14.3 ± 10.4% and femoral neck BMD increased by 4.5 ± 10.7%. In the younger subgroup, lumbar spine BMD significantly increased by 12.2 ± 8.5% and femoral neck BMD increased by 2.9 ± 8.3%. In the older subgroup, the mean absolute lumbar spine BMD change was 0.111 ± 0.071 g/cm^2 and femoral neck BMD change was 0.019 ± 0.043 g/cm^2. In the younger subgroup, the mean absolute lumbar spine BMD change was 0.098 ± 0.065 g/cm^2 and femoral neck BMD change was 0.016 ± 0.045 g/cm^2. The absolute increases in PINP and urinary NTX were similar between the subgroups. The authors concluded that teriparatide is effective independent of age and individuals beyond 80 years of age benefit from treatment (67).

In conclusion, the available data do not indicate that the efficacy of teriparatide is significantly influenced by the patients' age.

Paediatric population
Matarazzo et al. (2014) evaluated the safety and efficacy in paediatric patients with genetically proven syndromic hypoparathyroidism, a rare endocrine disorder. Six paediatric patients (four males, two females, age 9.8 ± 5.1 years) with syndromic hypoparathyroidism (including three with autoimmune polyendocrinopathy candidiasis ectodermal dysplasia syndrome, two with DiGeorge syndrome, and one with hypoparathyroidism-deafness-renal dysplasia syndrome) were included, follow-up lasted a mean of 2.5 years. Use of teriparatide (12.5 µg twice daily) was compared to conventional treatment based on oral administration of calcium plus oral calcitriol. Teriparatide treatment allowed complete calcium and vitamin D withdrawal in two patients, calcium withdrawal in three patients and reduction of vitamin D dose in two patients. Mean blood calcium, phosphorus, and alkaline phosphatase were not significantly modified, whereas significant reduction of the calciuria-to-creatininuria ratio was obtained. Tolerability was rated as very good; growth was normal in all patients. Both therapeutic adherence and perceived quality of life improved according to parents' opinion. The number of tetanic episodes was reduced in four patients during teriparatide treatment compared to conventional treatment. The authors stated that teriparatide is a promising new treatment of chronic hypocalcaemia in hypoparathyroid syndromic children (57).

According to the proposed SmPC, the safety and efficacy of teriparatide in children and adolescents less than 18 years has not been established. The product should not be used in paediatric patients or young adults with open epiphyses. Of note, treatment of hypoparathyroidism is not an indication of the product under discussion.

Premenopausal women

Cohen et al. (2015) reported on the use of teriparatide in normally menstruating premenopausal women with idiopathic osteoporosis. Twenty-one women enrolled in an open-label pilot study of teriparatide (20 μg for 18 - 24 months) had substantial BMD increases at the lumbar spine (10.8 ± 8.3%), total hip (6.2 ± 5.6%), and femoral neck (7.6 ± 3.4%). Follow-up data was collected on 15 women who had gained 11.1 ± 7.2% at lumbar spine and 6.1 ± 6.5% at total hip, were premenopausal at teriparatide completion and continued without antiresorptive treatment. When BMD was remeasured 2.0 ± 0.6 years after teriparatide cessation, it declined by 4.8 ± 4.3% ($p = 0.0007$) at the lumbar spine. In contrast, BMD remained stable at the femoral neck (-1.5 ± 4.2%) and total hip (-1.1 ± 3.7%). Those who sustained lumbar spine bone loss > 3% (-7.3 ± 2.9%; $n = 10$) did not differ from those with stable lumbar spine BMD (0.1 ± 1.1%; $n = 5$) with regard to baseline BMI, BMD at any site or duration of follow-up, but were significantly older at re-evaluation (46 ± 3 vs. 38 ± 7; $p = 0.046$), had larger increases in lumbar spine BMD during teriparatide treatment and higher cancellous bone remodelling on transiliac biopsy at baseline and completion of teriparatide treatment. Serum bone turnover markers did not differ at baseline or teriparatide completion, but tended to be higher at the re-evaluation time point in those with post-teriparatide bone loss. These findings indicate that premenopausal women with idiopathic osteoporosis, particularly those over 40, may benefit from antiresorptive treatment to prevent bone loss after teriparatide (11).

Treatment with teriparatide in premenopausal women should only be initiated if the benefit clearly outweighs risks in this population (G1).

Pregnancy-related osteoporosis

Pregnancy-related osteoporosis is a rare disorder with potentially severe consequences: chronic pain and irreversible static disorders of the spine after vertebral fractures in young women. The mechanism of loss of bone mineral in some pregnant women is poorly understood. Vertebral fractures occur mainly during the last trimester of pregnancy and may be due to this mineral bone loss and mechanical stress. A retrospective, multicentre study involving 52 patients was carried out to define the causes and characteristics of pregnancy-related osteoporosis. The patients' mean age at time of fracture was 32.1 years. In 10 patients, the fractures had occurred during the last trimester of pregnancy, and in 36 at the time of delivery or during the first 2 months post-partum. The mean number of vertebral fractures was 3.8 ± 2.0. Thirty-three patients had a risk factor of low bone mass before pregnancy. Twelve had disorders or treatments (heparin) that might promote osteoporosis during pregnancy, while 14 had no trigger factors before or during pregnancy. Overall, phosphate and calcium levels were normal, except for hyperphosphoraemia in lactating women (90%). On DXA scan, osteoporosis predominated in the trabecular bone (spinal T-score - 3.4, hip T-score - 2). Nineteen patient received bisphosphonates for up to 3 years and eleven patients were treated with teriparatide over 18 months. Only 10 patients had a repeat fracture, and the increase in BMD during follow-up was considerable, and improved by bisphosphonates (annual gain + 10% in the spine) or teriparatide (+ 15%) (49).

According to the proposed SmPC, experience in premenopausal women is limited. Treatment should only be initiated if the benefit clearly outweighs risks in this population.

Diabetes mellitus type 2
Despite evidence for higher fracture risk, clinical effects of osteoporosis treatments in type 2 diabetes mellitus (T2D) are largely unknown. The observational Direct Analysis of Non-vertebral Fractures in the Community Experience (DANCE) osteoporosis study explored skeletal outcomes in over 4000 ambulatory female and male patients with osteoporosis. Patients received teriparatide 20 µg/day up to 24 months and were followed by observation up to 24 months. The incidence of new non-vertebral fragility fractures significantly decreased for patients receiving teriparatide for > 6 months. A *post hoc* analysis of the DANCE study assessed the effect of teriparatide in T2D patients compared with non-diabetic patients. Analyses included 4042 patients; 291 with T2D, 3751 without diabetes. Treatment exposure did not differ by group. For T2D patients, fracture incidence was 3.5 per 100 patient-years during 0 - 6 months treatment, and 1.6 during 6 months to treatment end (47% of baseline, 95% CI: 12, 187%); during similar periods, for patients without diabetes, fracture incidence was 3.2 and 1.8 (57% of baseline, 95% CI: 39, 83%). As determinants of fracture outcome during teriparatide treatment, diabetes was not a significant factor ($p = 0.858$), treatment duration was significant ($p = 0.003$), and the effect of duration was not significantly different between the groups (interaction $p = 0.792$). Increases in spine and total hip BMD did not differ between groups; increase in femoral neck BMD was greater in T2D patients than in patients without diabetes (+0.34 and +0.004g/cm^2, respectively; $p = 0.014$). Back pain severity decreased in both groups. Teriparatide was well tolerated without new safety findings (80).

Adult women with anorexia nervosa
Low BMD / osteoporosis is common in women with anorexia nervosa and the risk for fractures is significantly increased. A clinical trial randomly assigned 21 women (mean age: 47 years) to teriparatide (20 µg, s.c.) or placebo. At 6 months, spine BMD increased significantly more with teriparatide (posteroanterior spine, 6.0% ± 1.4%; lateral spine, 10.5% ± 2.5%) compared with placebo (posteroanterior spine, 0.2% ± 0.7%, $p < 0.01$; lateral spine, -0.6% ± 1.0%; $p < 0.01$). The results remained significant after controlling for baseline BMI, P1NP and IGF-1. Changes in femoral neck ($p = 0.4$) and total hip ($p = 0.8$) BMD were comparable in both groups, as were changes in weight. Serum P1NP levels increased after 3 months of teriparatide treatment and remained at this higher level at 6 months, whereas P1NP levels were unchanged in the placebo group ($p = 0.02$). Teriparatide was well tolerated by all subjects (27).

2.5.4.9 Efficacy in disorders other than osteoporosis

Fracture healing
Animal data indicated that daily s.c. injections of teriparatide increase callus formation, speed of fracture repair, and mechanical strength but data in humans is currently inconsistent. A retrospective observational study evaluated the effects of teriparatide on clinical outcomes and radiological findings of sacral insufficiency fractures in 7 elderly women administered for about 6 months. At their initial clinic visit, 6 patients could neither walk nor sit. Computed tomography (CT) images revealed sacral wing fracture in 6 patients, and bone scintigram showed H-shaped uptake over the bilateral sacral wings in one patient. After six months of therapy, 5 patients were able to walk. Mean visual analogue scale score was significantly lower after (12.9 mm) than before (87.4 mm) teriparatide treatment ($p < 0.0001$). CT images revealed bone union (4 patients) and sclerotic changes (3 patients) at the fracture sites (41).

In a recent meta-analysis based on an extensive literature search in PubMED, the Cochrane Library and EMBASE evaluating teriparatide's potential to support fracture healing, Shi et al.

(2016) found that a significant effectiveness with regards to function improvement in patients following fracture has been documented. However, there was no significant effectiveness with regards to time of radiographic fracture healing, fracture healing rate and reduction in pain (81).

Osteogenesis imperfecta
Osteogenesis imperfecta is a genetic disorder due to collagen defect, mostly caused by mutations of the genes coding the chains of collagen type 1. Symptoms include low bone mass, increased bone fragility, low-trauma fractures, short stature and skeletal deformities. The bisphosphonate neridronate has been studied in controlled trials both in children and adults with evidence of a significant 64% decrease in fracture number. A randomised, double-blind prospective study evaluated teriparatide versus neridronate in patients (n = 98, > 25 years of age) with osteogenesis imperfecta type I over a 24-month observation period. New fragility fractures developed in fewer patients in the teriparatide group than in the neridronate group although this difference was not significant (8 [16.3%] vs. 13 [26.5%], respectively, p = 0.10). Bone pain and overall health scores significantly improved following treatment with both drugs ($p < 0.001$) with better outcomes using teriparatide than neridronate. According to the authors, teriparatide has a promising role of in the therapy of osteogenesis imperfecta type I (50).

Hypoparathyroidism
Until the safety concern of oncogenesis is completely ruled out, long-term treatment of hypoparathyroidism with teriparatide is not an acceptable therapeutic option. However, short-term management of postoperative hypoparathyroidism has been studied in patients with extensive head and neck surgical procedures for invasive thyroid, pharyngeal or laryngeal carcinoma. Hospital stays are routinely prolonged because of the lag between initiation of vitamin D and calcium therapy, and normalisation of serum calcium. Initial findings warrant the further exploration of teriparatide, possibly permitting a more gradual and safe escalation of calcium and vitamin D therapy in these patients (83).

2.5.5 Overview of safety

2.5.5.1 Adverse effects characteristic with the management of osteoporosis

In the treatment of osteoporosis, a number of drugs with different modes of action are employed. Bisphosphonates, the most commonly used drugs, as well as calcitonin, oestrogen, SERMs and RANKL inhibitors decrease the activity of osteoclasts, thereby inhibiting bone resorption. Recently, concerns have been raised regarding the prolonged use of these drugs as they interfere with normal bone turnover, preventing local micro-damage from normal mechanical loading or injury being repaired which may ultimately result in bone necrosis. Teriparatide has a unique mode of action as it treats osteoporosis by stimulating new bone formation.

Khan et al. (2017) reviewed and summarised important features of the safety profiles of commonly used drugs in the treatment of osteoporosis:

- Bisphosphonates and denosumab are effective in reducing the risk of vertebral, non-vertebral, and hip fracture and are well tolerated with only minor side effects with short-term use.
- Long-term use of bisphosphonates and denosumab is associated with a small increased risk of atypical femoral fracture and rarely osteonecrosis of the jaw (ONJ); these

uncommon adverse events can be prevented or identified early with close monitoring and patient education.

- Teriparatide, an anabolic agent, is effective in reducing the risk of vertebral and non-vertebral fracture and is well tolerated with minor side effects.
- Raloxifene is effective in lowering the risk of vertebral fracture only and is associated with hot flushes and an increased risk of thromboembolic events.

The authors concluded that in the absence of contraindications the benefits of currently authorised anti-osteoporosis drugs are far greater than the potential risk of therapy. Selecting the best medication for each patient requires a review of the individual fracture risk as well as drug suitability with respect to potential adverse effects. The risk for long-term adverse effects can be minimised by close follow-up of the patient (43).

Similar conclusions were drawn by Varenna et al. (2013) and Rossini et al. (2016) based on systematic reviews of the literature. The safety profile of currently available drugs for the treatment of osteoporosis is well defined. Side effects are infrequent and predictable, and severe adverse effects are very rare. For medications currently authorised, the benefits derived from the reduced incidence of fractures, and the consequent reduction in mortality and disability, significantly exceed the risk of side effects (76, 88).

2.5.5.2 Adverse effects characteristic of teriparatide

The toxicity profile of teriparatide has been well established; at therapeutic dosing, it has been found to be predictable and well tolerated with favourable safety.

In the Fracture Prevention Trial, postmenopausal women with osteoporosis and prevalent fractures were randomised to receive once-daily s.c. injections of teriparatide 20 µg (n = 541), teriparatide 40 µg (n = 552) or placebo (n = 544) over a mean duration of 21 months. There were no significant differences among the three groups with respect to the numbers of deaths and hospitalisations or the numbers of women in whom cardiovascular disorders, urolithiasis or gout developed during the study. There were no cases of osteosarcoma. Cancer developed in 40 women, with a higher incidence in the placebo group (4%) than in the 20-µg and 40-µg active treatment groups (2% in each group). A total of 32 women in the placebo group (6%), 35 in the 20-µg group (6%), and 59 in the 40-µg group (11%) withdrew from the study because of an adverse event (AE). Nausea was reported by 18% of women taking 40 µg teriparatide, and headache was reported by 13%, whereas only 8% of women taking placebo reported each of these symptoms ($p < 0.001$ and $p = 0.01$, respectively); the frequencies of nausea and headache in the 20-µg group were similar to those in the placebo group. Nine percent of the women in the 20-µg group reported dizziness and 3% percent reported leg cramps, but these symptoms were reported by only 6% and 1% of women in the placebo group, respectively ($p = 0.05$ and $p = 0.02$, respectively); the frequencies of dizziness and leg cramps in the 40-µg group were similar to those in the placebo group. Pre-injection blood pressure and heart rate, measured at each visit, were unaffected by treatment with teriparatide (65).

In 2006, the prospective European Forsteo Observational Study (EFOS) was set up to observe the effects of teriparatide treatment for up to 18 months, with a posttreatment follow-up period of a further 18 months' duration, in postmenopausal women (n = 1648, mean age [SD] 71.5 [8.4] years). The patients prescribed teriparatide in the EFOS were severely osteoporotic, with a high fracture risk and poor HRQoL, despite previous therapy for osteoporosis; moderate to severe back pain was also very common. There were 365 adverse events (AEs) spontaneously

reported; of these, 135 (37%) were serious and 175 (48.0%) were considered related to teriparatide; AEs were the reason for discontinuation for 79 (5.8%) patients. The most common AEs were nausea (5.5%), headache (4.4%), fatigue and depression (2.7% each). There were four spontaneous reports of hypercalcaemia, one of which was considered severe as it resulted in prolonged hospitalisation. There were 27 deaths during the study period, representing 1.6% of the EFOS cohort. The treating physicians did not consider any death to be drug-related and it was concluded that safety was consistent with the prescribing information (48).

Of the 1611 enrolled patients in the prospective, extended Forsteo Observational Study (ExFOS), 173 (10.7 %) had at least one AE and 120 (7.4 %) had at least one serious AE during the active treatment phase. Of the 339 AEs reported, 211 (62.2 %) were serious and 57 (16.8 %) were considered possibly related to study medication. The most common AEs (> 2 %) reported were fall (7.1%), nausea (4.1%) and headache (2.9 %). No cases of osteosarcoma were observed during the 24-month teriparatide treatment phase. There were 34 patients with at least one AE leading to death (2.1% of all 1611 enrolled patients); none of these deaths were considered related to the study drug by the reporting investigators (47).

Varenna et al. (2013) reviewed the literature on the safety of drugs used in treatment of osteoporosis; with respect to teriparatide, tolerability and safety are very good. A transient increase of serum calcium levels with a peak 4 - 6 hours postdose and a reduction to basal levels are reached long before the following day administration. These serum calcium variations usually remain in the normal range; only in 11% of patients a slight hypercalcaemia was observed in pivotal trials. Repeated or persistent hypercalcaemia suggest a reassessment of the diagnosis and eventually the reduction or interruption of calcium supplementation. A dose reduction of teriparatide is rarely necessary. An increase in calcium renal excretion (about 30 mg in 24 hours) has been observed but without clinical manifestations. However, patients with a history of hypercalciuria or nephrolithiasis in the previous 5 years were generally excluded from clinical trials and an increase of serum uric acid has been reported uncommonly. Caution is advised in patients with a history of urolithiasis and/or gout. In clinical trials, nausea, dizziness / vertigo, leg cramps and an injection site reaction have been reported with a higher frequency than placebo (88).

Carcinogenesis
In initial preclinical studies in rats administered teriparatide, a dose-dependent increase in the risk of osteosarcoma incidence was observed. Osteosarcoma in humans is a primary malignant bone tumour. However, the incidence of osteosarcoma in patients with chronic primary or secondary hyperparathyroidism is not increased despite increased osteoblast activity. Although subsequent studies demonstrated a ‘‘no-effect’’ dose in rats and no bone tumours were seen in a long-term study of cynomolgus monkeys (86, 87), osteosarcoma is a potential risk as long an association with teriparatide use in humans cannot be completely ruled out (G1, G2).

To address a putatively increased risk of osteosarcoma in subjects exposed to teriparatide, surveillance studies were designed in which adult cases of osteosarcoma are identified by participating population-based cancer registries and participating medical centre cancer registries. Exposure to teriparatide is ascertained through interview and compared with the expected rate of exposure in this population to identify any potential signal of an increased risk of osteosarcoma.

The US Osteosarcoma Surveillance Study, an ongoing surveillance study initiated in 2003, is a postmarketing commitment to the FDA to evaluate a potential association between teriparatide

and development of osteosarcoma. Between June 2004 and September 2011, 1448 cases (diagnosed 2003 to 2009) were identified by participating cancer registries (estimated to be 62% of all adult cases in the US for that time period); 549 patients or proxies were interviewed. Interviewed patients were similar to non-interviewed patients with regard to mean age, sex, race and geographical distribution and tumour type and site of tumour. Mean age of those interviewed was 61 years, 46% were female, 86% were white and 77% were alive when the case was reported to the study investigators. After 7 years of the study, there were no osteosarcoma patients who had a prior history of teriparatide treatment (2). An additional measure is the Forteo Patient Registry (FPR) that also aims to estimate the incidence of osteosarcoma in US patients treated with teriparatide. The prospective US registry was established in 2009; enrolment is planned for 10 years (up to 2019) and annual linkage with US state cancer registries for 15 years (up to 2024). For the most recent annual linkage in 2017, information necessary for linkage with 63,270 patients in the FPR was submitted to each of the 42 participating registries. These patients contributed approximately 242,782 person-years of follow-up. A total of 5268 adult osteosarcoma cases diagnosed since 2009 were available for linkage from participating state cancer registries. To date, no incident cases of osteosarcoma have been identified among patients registered in the FPR (30).

Cases in which patients developed osteosarcoma in temporal relationship with teriparatide therapy for osteoporosis are extremely rare and causal association is doubtful: A 70-year-old woman with a complex past medical history was found to have metastatic cancer in the second year of teriparatide therapy for osteoporosis with vertebral fractures. The patient subsequently died, no autopsy was performed, the primary cancer site was never identified but osteosarcoma was suggested (35). A 67-year-old man with a history of prostate cancer and radiation therapy to the prostatic bed was diagnosed with chondroblastic osteosarcoma of the left pubic ramus two months after initiation of teriparatide for osteoporosis (82). At the time of the latter report, it was estimated that more than 430,000 subjects had received teriparatide for treatment of osteoporosis. In both cases, an additive effect of teriparatide cannot be completely ruled out and thus contraindications including Paget's disease of bone, unexplained elevations of alkaline phosphatase, open epiphysis, or prior external beam or implant radiation therapy involving the skeleton must be adhered to (G1). Lindsay et al. (2016) mentioned a third report; however, here osteosarcoma was probably pre-existing since enlargement of a mass was noted prior to initiation of teriparatide (52).

Evaluation of particular adverse effects

Hypercalcaemia
With once-daily dosing of teriparatide, serum calcium concentrations transiently increase beginning approx. 2 hours following dosing and reach a maximum concentration between 4 and 6 hours following dosing (median increase 0.4 mg/dL). Six hours following dosing, serum calcium levels begin to decline and return to baseline 16 - 24 hours after each dose (10).

A detailed analysis of potential hypercalcaemia was performed in the Fracture Prevention Trial. All enrolled women (n = 1637) received daily supplements of 1000 mg of calcium and 400 to 1200 IU of vitamin D. Serum calcium was measured before and 4 to 6 hours after injection at baseline and after 1, 3, 6, 12, 18 and 24 months of treatment. The preinjection measurements (performed 16 to 24 hours after the previous injection) were usually normal. Mild hypercalcaemia (defined as a calcium concentration that exceeded 10.6 mg/dL [2.6 mmol/L]) occurred at least once in 2% of the women in the placebo group, 11% of those in the 20-µg parathyroid hormone group and 28% of those in the 40-µg group. If the post-injection serum

calcium concentration was high or if urinary excretion of calcium exceeded 350 mg (8.8 mmol) per day, and if the increase persisted on repeated testing, the calcium supplement was discontinued permanently, or the volume of the injected study drug was halved until the abnormality had disappeared. Persistent hypercalcaemia after a reduction in calcium intake occurred in 3 women in the placebo group (< 1%), 15 in the 20-µg group (3%) and 62 in the 40-µg group (11%). Treatment was withdrawn because of repeatedly elevated serum calcium concentrations in one woman in the placebo group, one in the 20-µg group and nine in the 40-µg group. Women who did not have hypercalcemia during the first six months of treatment seldom had it later (65).

Based on pharmacokinetic data derived from the Fracture Prevention Trial, Satterwhite et al. (2010) examined whether the transient increases in serum calcium values (4 - 6 hours postdose) were associated with any clinical adverse effects commonly associated with hypercalcaemia. Adverse events in patients in the teriparatide group who had elevated (10.6 mg/dL) postdose serum calcium were summarised in comparison with the overall cohort of patients (receiving teriparatide 20 µg/day). Although the analysis may be limited due to the low number of cases, there were no specific safety findings possibly associated with hypercalcaemia (79).

Table 2: Adverse events commonly seen in patients treated with teriparatide who had elevated postdose serum calcium levels in comparison with the overall cohort of patients in the teriparatide group (79)

	Overall cohort[a] ($n = 541$)	Patients[a] with serum Ca > 10.6 ($n = 50$)
Neurological		
Headache		
Depression		
Gastrointestinal		
Abdominal pain		
Pancreatitis		
Nausea		
Anorexia		
Constipation		
Vomiting		
Peptic ulcer/gastritis		
Cardiovascular		
Arrhythmias		
Hypertension		

[a] *n* (%)

Hypomagnesaemia

Bégin et al. (2018) aimed to determine the incidence of hypomagnesaemia (serum magnesium < 0.7 mmol/L) associated with teriparatide in a retrospective cohort and to identify putatively predisposing factors to hypomagnesaemia. The authors reviewed files of 53 patients treated for severe osteoporosis with teriparatide for 6 to 24 months between years 2008 and 2016. Serum magnesium levels were measured at baseline and at 3, 6, 12, 18 and 24 months. In the full cohort, an average decrease of serum magnesium of 0.075 mmol/L, 0.069 mmol/L, 0.085 mmol/L, 0.086 mmol/L ($p < 0.001$) at 3, 6, 12 months and at the end of the treatment, respectively, was observed. The cumulative incidence of hypomagnesemia during treatment with teriparatide was 35.9% (19 patients). Patients' older age (71.1 versus 65.1 years; $p = 0.05$)

and lower baseline level of magnesium before teriparatide treatment (0.81 mmol/L versus 0.85 mmol/L; p = 0.03) were significant risk factors for teriparatide-associated hypomagnesaemia. The average decrease of serum magnesium was greater in the patients who developed hypomagnesemia compared with normomagnesemic patients at 3 months (0.110 mmol/L versus 0.054 mmol/L; p = 0.02), 6 months (0.139 mmol/L versus 0.036 mmol/L; p < 0.001) and 12 months (0.156 mmol/L versus 0.048 mmol/L; p < 0.001). Serum calcium, creatinine and parathyroid hormone remained normal throughout the treatment period. Clinical symptoms associated with hypomagnesaemia were not observed. None of the patients had to stop therapy because of their magnesium level and thus clinical significance is unknown (3).

Effects on glucose metabolism

As there is some indirect evidence of an unfavourable effect of PTH on glucose metabolism (e.g., ~ 40% of patients with primary hyperparathyroidism have impaired glucose tolerance), a prospective study evaluated the acute and chronic effect of teriparatide administration (20 µg per day over six months) on serum glucose and insulin levels in women with established osteoporosis (n = 23; mean age 65.6 ± 1.8 years). There were significant differences between the oral glucose tolerance tests (OGTT)-basal and OGTT-acute values in glucose at 90 min (168.3 ± 9.8 vs. 180.6 ± 9.2, p < 0.05) and 120 min (152.0 ± 8.7 vs. 170.5 ± 7.8, p < 0.01), between the OGTT-basal and OGTT-chronic values for glucose at 90 min (168.3 ± 9.8 vs. 184.5 ± 13.3, p < 0.05) and between the OGTT-basal and OGTT-acute for insulin at 90 min (56.7 ± 7.4 vs. 68.7 ± 8.2, p < 0.01). These differences remained significant for the subgroup of patients with normal (n = 8) but not impaired glucose tolerance or diabetes mellitus (n = 15). In conclusion, teriparatide seems to have an acute, subclinical adverse impact on stimulated glucose levels, possibly due to insulin resistance. However, this effect subsides with prolonged treatment and clinical relevance is unlikely at present (1).

Cardiac safety

It is known that an increased occurrence of cardiovascular disease (CVD) is seen in patients with primary hyperparathyroidism. The N-terminal fragment of the pro-peptide of brain natriuretic peptide (NT-proBNP) is an accepted risk marker of CVD, has been shown to be elevated in patients with primary hyperparathyroidism. Ellegaard et al. (2012) investigated whether teriparatide treatment is associated with changes in plasma NT-proBNP. A total of 42 patients (10 men and 32 women, mean age 68 years) receiving teriparatide were included in the study. Blood samples were taken at baseline, and after 1, 3 and 6 months of treatment. Plasma concentrations of NT-proBNP were measured. Plasma concentrations of ionised calcium, PTH and alkaline phosphatase (ALP) were also analysed, and BMD for the lumbar spine and total hip was recorded at baseline and after 6 months. No effect of teriparatide on plasma concentrations of NT-proBNP was observed at any time points. Ionised calcium and ALP concentrations in the plasma increased after 6 months of treatment, whereas PTH concentrations decreased. Spine BMD T-score was significantly increased after 6 months of treatment. These findings suggest that intermittent exposure to therapeutic levels of teriparatide does not affect heart function (23).

Immunogenicity

In published findings of controlled and observational studies, a clinically relevant immunogenic potential of teriparatide was not detected (28, 65). Given the low molecular weight of the peptide and the lack of posttranslational modifications, the immunogenic potential of teriparatide is low and, furthermore, there are no concerns on immunogenicity based on the available postmarketing data. Reports on allergic reactions / anaphylaxis possibly associated

with teriparatide are rare and there is no evidence for hypersensitivity (i.e. generation of antibodies) against teriparatide as regards the originator product (G2, G3).

The synthetic and recombinant versions of teriparatide share an identical amino acid sequence, representing the biologically active, N-terminal, 1-34 sequence of human parathyroid hormone (which has 84 amino acids total).

When comparing peptides obtained by different processes (chemical or recombinant):

- The related peptides (which are molecules with a chemical structure very similar to the API) should not involve any difference in the safety of the product.
- Differently than products obtained by chemical synthesis, products obtained by biological processes have a real risk for immunogenicity as described in the ICH S6 guideline as follows:

  "*…there are potential risks associated with host cell contaminants derived from bacteria, yeast, insect, plants, and mammalian cells. The presence of cellular host contaminants can result in allergic reactions and other immunopathological effects. The adverse effects associated with nucleic acid contaminants are theoretical but include potential integration into the host genome. For products derived from insect, plant and mammalian cells, or transgenic plants and animals there may be an additional risk of viral infections*".

Therefore, teriparatide obtained by chemical synthesis do not have a specific contribution for immunogenicity because no contaminants from biological origin will be present in the product. Moreover, the low intrinsic immunogenicity of / high immune tolerance for a synthetic human parathyroid hormone 1-34 peptide was evident from the need to include Freund's complete adjuvant, in addition to immunisation with bovine parathyroid hormone peptides, in order to break B-cell tolerance and induce antibodies reactive with synthetic human parathyroid 1-34 (6).

The recombinant version of teriparatide has been associated with a relatively low level of detectable, treatment-emergent, anti-drug antibodies: The EMA Scientific Discussion for the European related product Forsteo states that anti-drug antibodies were detected in only 4% of treated subjects, and these were without any apparent clinical impact, not affecting either the BMD response or serum calcium concentrations (G2)**.**

According to the Australian Public Assessment Report for Forteo it is stated: *"In a large clinical trial, antibodies that cross-reacted with teriparatide were detected in 2.8% of female patients receiving Forteo. Generally, antibodies were first detected following 12 months of treatment and diminished after withdrawal of therapy. There were no hypersensitivity reactions, allergic reactions, effects on serum calcium or effects on BMD response, which indicates that the antibodies did not cause any clinically significant adverse effects."* (G6).

Neither the Risk Evaluation and Mitigation Strategy (REMS), approved by FDA (G7) as part of the US approval of recombinant teriparatide, nor the Forteo registry, that was a post-marketing commitment (2), feature any monitoring of immunogenicity.

In addition to the low incidence of drug-induced immunogenicity, there is no evidence that these possible antibodies have a clinical relevance. The relatively low incidence of detection of antibodies to Forteo, allied to slow time-course of antibody formation, implies a low sensitivity

to detect possible differences in immunogenicity of different versions of teriparatide in controlled clinical studies. The absence of any reported clinical correlates of undesirable immunogenicity to teriparatide could preclude a judgment of clinical relevance of any differences in antibody formation observed.

It can be concluded that the intrinsic immunogenicity associated with teriparatide (synthetic or recombinant) should be considered negligible.

2.5.5.3 Safety evaluation in special populations

Renal impairment
Since there are no data on the use of teriparatide in patients with severe renal impairment, the drug is contraindicated in these patients. Caution is warranted in those with moderate renal impairment (G1).

Miller et al. (2006) explored the incidence of AEs and the BMD and fracture reduction responses to teriparatide in women with age-related mild (eGFR 50 - 79 mL/min) or moderate (eGFR 30 - 49 mL/min) renal impairment. In this double-blinded trial, 1637 ambulatory postmenopausal women (ranging in age from 42 to 86 years) were randomised to placebo (n = 544), teriparatide 20 µg/day (n = 541) or teriparatide 40 µg/day (n = 552) with daily calcium (1000 mg) and vitamin D (400 - 1200 IU) supplementation. Compared with patients with normal renal function, patients with renal impairment were older, shorter, weighed less, had been postmenopausal longer, and had lower baseline lumbar spine and femoral neck BMD. Compared with placebo, teriparatide significantly increased PINP and lumbar spine and femoral neck BMD within each renal function subgroup, and there was no evidence that these increases were altered by renal insufficiency (each treatment-by-subgroup interaction $p > 0.05$). Similarly, teriparatide-mediated vertebral and non-vertebral fracture risk reductions were similar and did not differ significantly between patients with normal or impaired renal function (treatment-by-subgroup interactions $p > 0.05$). The incidences of treatment-emergent and renal-related AEs were consistent across treatment assignment in the normal, mildly impaired, and moderately impaired renal function subgroups. Teriparatide induced changes in mean eGFR were unaffected by baseline renal function (treatment-by-renal function interaction $p > 0.05$ for normal, mildly impaired or moderately impaired subgroups). Patients in all renal function categories treated with teriparatide 20 or 40 µg/day had an increased incidence of 4 - 6-hour postdose serum calcium >10.6 mg/dL (the upper limit of normal) versus placebo; however, teriparatide 20 µg/day was not associated with significantly increased incidence of 4 - 6-hour postdose serum calcium >11 mg/dL in any renal function category. Teriparatide therapy was associated with increased incidence of elevated uric acid, with the incidences being highest in patients with moderately impaired renal function and in those receiving teriparatide at 40 µg/day. Even so, AE data did not suggest an increased incidence of gout or arthralgia or of nephrolithiasis events in teriparatide-treated patients with normal, mild or moderate renal impairment (60).

Nishikawa et al. (2016) conducted a *post hoc* analysis of a prospective postmarketing surveillance study that included patients with osteoporosis at high risk of fracture and severe stages of chronic kidney disease (CKD). Among 1882 patients enrolled, 33 patients suffered from severe CKD (i.e. eGFR of 15 - 29 mL/min per 1.73 m^2, stage 4, n = 30 and end-stage renal failure, stage 5, n = 3). All patients were female and 81.8% had a history of previous fracture. Teriparatide demonstrated positive effects on bone formation and key markers independent of

renal function. No serious adverse drug reactions (ADRs) were recorded; a total of 4 ADRs (hyperuricaemia, renal dysfunction, injection site warmth and headache) were recorded for 4 of 33 patients. New fractures occurred in one patient with stage 5 CKD, but not in patients with stage 4 CKD. In this study, patients severe CKD had a positive response in terms of effectiveness and no additional safety concerns were observed (68).

Elderly
In a retrospective study, Niimi et al. (2016) compared the efficacy and tolerability of daily teriparatide therapy in patients with established osteoporosis with respect to age (≥ 80 years and < 80 years). Treatment was well tolerated in elderly patients and no significant difference in the safety profile between the patients' age groups were noted (67).

Pregnancy
There are no data on the safety of teriparatide in pregnant women. Teriparatide is contraindicated for use during pregnancy; women of childbearing potential should use effective methods of contraception if treated with teriparatide (G1).

2.5.5.4 Relation of adverse events to dose, dose regimen and treatment duration

No relevant data of adverse events in relation to dose, dose regimen and treatment duration have been detected. In placebo-controlled dose findings studies, AEs were more pronounced with the 40-µg dose, but most events were observed with similar frequency between the 20-µg dose group and the placebo group (65) (G2).

2.5.5.5 Long-term safety

There are no particular safety concerns associated with the prolonged use of teriparatide. However, the use of teriparatide is currently restricted to a maximum total duration of 24 months due to the potential risk of osteosarcoma (see also section 2.5.5.2). Carcinogenesis was noted in rodents with long-term administration but not in primates. Although there is currently no evidence neither from clinical studies nor from more than 15 years of postmarketing experience nor from patient registries that teriparatide has an oncogenic potential in humans, osteosarcoma is still assessed as a potential risk (30, 52) (G1, G2).

2.5.5.6 Relevant *in vitro* and animal toxicology

Mutagenicity, genotoxicity and carcinogenicity
Teriparatide was not genotoxic in any of the following test systems: the Ames test for bacterial mutagenesis, the mouse lymphoma assay for mammalian cell mutation, the chromosomal aberration assay in Chinese hamster ovary cells, with and without metabolic activation and the *in vivo* micronucleus test in mice (G1, G2).

In initial preclinical studies in rats administered teriparatide, a dose-dependent increase in the risk of osteosarcoma incidence was observed (2, 86). Additional studies in rats and cynomolgus monkeys indicated that teriparatide will likely not cause the formation of osteosarcoma in humans (87). There is evidence that the rodent skeleton is more sensitive to the pharmacological effects of PTH on the formation of new bone than primate

skeletons. Nevertheless, based on the rat toxicology findings, teriparatide should not be used in patients at high risk for osteosarcoma, including those with metabolic bone diseases such as hyperparathyroidism and Paget's disease of the bone (G1, G2).

2.5.5.7 Methods to prevent, mitigate or manage adverse events

Contraindications
The use of teriparatide is contraindicated

- in case of hypersensitivity to the active substance or to any of the excipients
- during pregnancy and lactation

and furthermore in patients

- with pre-existing hypercalcaemia
- with metabolic bone diseases (including hyperparathyroidism and Paget's disease of the bone) other than primary osteoporosis or glucocorticoid-induced osteoporosis
- with unexplained elevations of alkaline phosphatase
- with severe renal impairment (creatinine clearance ≤ 50 mL/min)
- with prior external beam or implant radiation therapy to the skeleton
- with skeletal malignancies or bone metastases

Of note, the safety and efficacy of teriparatide in children and adolescents less than 18 years has not been established. The agent should not be used in paediatric patients (less than 18 years old), or young adults with open epiphyses.

Special warnings / precautions
Following the administration of teriparatide to normocalcaemic patients, slight and transient elevations of serum calcium concentrations have been observed injection. Serum calcium concentrations reach a maximum between 4 and 6 hours and return to baseline by 16 to 24 hours after each dose of teriparatide. Routine calcium monitoring during therapy is not required but if blood samples for serum calcium measurements are taken, this should be done at least 16 hours after the most recent injection. In clinical trials, the incidence of hypercalciuria with teriparatide did not differ from that with placebo but small increases in urinary calcium excretion may occur (73).

Teriparatide should be used with caution in patients with active or recent urolithiasis because of the potential to exacerbate this condition.

In short-term clinical studies with teriparatide, isolated episodes of transient orthostatic hypotension were observed.

Caution is advised in patients with moderate renal impairment.

Experience in the younger adult population, including premenopausal women, is limited. Treatment should only be initiated if the benefit clearly outweighs risks in this population.

Since an increased risk of osteosarcoma with long-term teriparatide use cannot be completely ruled out, treatment duration should not exceed 24 months.

Drug interactions
There is currently no evidence of clinical relevant drug interactions when teriparatide is used concomitantly with other medications.

Clinical studies did not indicate pharmacodynamic interactions of teriparatide with oral hydrochlorothiazide or intravenous furosemide (73) (G1).

Concurrent use of raloxifene or hormone replacement therapy with teriparatide did not alter effects on serum or urine calcium nor predispose to clinical AEs (G1).

Fertility, pregnancy and lactation
Teriparatide should not be used in pregnant women because the peptide has not been studied in human foetal development. Women of childbearing potential should use effective methods of contraception when using teriparatide. If pregnancy occurs, teriparatide should be discontinued. There are no clinical data to determine whether teriparatide is secreted into breast milk. Thus, the drug also should not be used in women who are breastfeeding (73) (G1).

Ability to drive and use machines
Teriparatide has no or negligible influence on the ability to drive and use machines. Transient, orthostatic hypotension or dizziness was observed in some patients. These patients should refrain from driving or the use of machines until symptoms have subsided (G1).

2.5.5.8 Reactions due to overdose, potential for dependence, rebound phenomena and abuse

Isolated spontaneous reports describing medication errors where the entire content (up to 800 µg) of a teriparatide pen have been administered as a single dose. Transient events reported have included nausea, weakness or lethargy and hypotension. In some cases, no adverse effects were observed. No fatalities associated with overdose have been reported (G1, G3).

The effects of overdose that might be expected include delayed hypercalcaemia and risk of orthostatic hypotension, nausea, vomiting, dizziness and headache (G1).

There is no potential for dependence, rebound phenomena and abuse.

2.5.5.9 World-wide marketing experience

Compliance with osteoporosis therapy is generally assessed as poor. Reyes et al. (2017) carried out a retrospective cohort study using a Spanish real-world population database to estimate the persistence to anti-osteoporosis drugs. A total of 19,253 women were included. Unadjusted 2-year persistence [95% CI] ranged from 10.3% [9.1, 11.6%] (strontium ranelate) to 45.4% [43.1, 47.8%] (denosumab). One-year persistence went from 35.8% [33.9%, 37.7%] (strontium ranelate) to 65.8% [63.6%, 68.0%] (denosumab). At the end of the first year and compared to alendronate users, both teriparatide and denosumab users had a reduced cessation risk (adjusted hazard ratio [HR]: 0.76, 95% CI: 0.67, 0.86 and 0.54, 95% CI: 0.50, 0.59 respectively). The

authors concluded while overall unadjusted persistence to treatment was insufficient, both teriparatide and denosumab users had significantly higher 1-year persistence compared to alendronate users. While unmeasured confounding by indication cannot be concluded, compliance in osteoporotic women treated with teriparatide and denosumab appeared to be higher than in those treated with alendronate (75).

Thorsteinsson et al. (2018) examined long-term benefits and risks of PTH treatment for osteoporosis based on data of the Danish national registers. In the study period (years 2003 - 2010), 3702 patients were exclusively treated with teriparatide and 579 were exclusively treated with recombinant PTH (1-84). In the study period, patients persistent with therapy for at least 18 months and with a medication possession rate > 0.8, 83% of the patients in the teriparatide group were compliant versus 72% in the recombinant PTH (1-84) group ($p < 0.01$). Being married/cohabiting, still in the labour market and taking teriparatide were significantly associated with higher compliance, whereas age, gender, level of education, income, alcoholism and comorbidity index were not associated with compliance. For comparison, patients treated with a bisphosphonate (n = 13,131) and anti-osteoporotic treatment-naïve controls (n = 12,721) were selected. Following PTH treatment in compliant patients, neither fracture incidence nor drug consumption differed between PTH-treated and bisphosphonate-treated patients, despite the fact that PTH-treated patients had more severe osteoporosis (T-score ≥ 3) No increased incidence of malignant diseases or other diseases (including depression, urolithiasis or cardiac disorders) was detected. The authors stated that their findings underline that PTH treatment is effective and safe (84).

A study by Burge et al. (2017) examined both the association and the real-world effectiveness of teriparatide treatment on the incidence of hip and other fractures in the United States based on 11 years of market experience using data from the Truven MarketScan Research Databases. Among 14,284 teriparatide-treated subjects, mean age was 68.4 years, 89.8% were female, and 29.6% had a fracture in the previous year; these characteristics were similar across adherence (medication possession ratio) and persistence groups. The effects of adherence and persistence to teriparatide were statistically significant ($p < 0.001$) for all fracture types except wrist ($p \geq 0.125$). By logistic regression, high versus low adherence was associated with reduced risk for any (OR: 0.67; $p < 0.001$); vertebral (OR: 0.64; $p < 0.001$); non-vertebral (OR: 0.71; $p < 0.001$) and hip fractures (OR: 0.52; $p < 0.001$) and longer (19 - 24 months) versus shorter persistence (1 - 6 months) was associated with reduced risk for any (OR: 0.63, $p < 0.001$); vertebral (OR: 0.56, $p < 0.001$); non-vertebral (OR: 0.69, $p < 0.001$) and hip fractures (OR: 0.48, $p < 0.001$). Cox models revealed a significantly reduced risk between high and low adherence for any (OR: 0.69, $p < 0.001$); vertebral (OR: 0.60, $p < 0.001$); non-vertebral (OR: 0.77, $p < 0.001$) and hip fractures (OR: 0.55, $p < 0.001$). In conclusion, findings demonstrate real-world effectiveness of teriparatide to reduce the risk of hip fractures along with other fragility fractures in the US. Among teriparatide patients in a US claims database who were observed for 2 years after teriparatide initiation, fracture incidence significantly decreased as adherence and persistence increased for vertebral, non-vertebral, hip, and any clinical fractures (8) .

Yoshiki et al. (2017) performed a post hoc analysis of a postmarketing surveillance study that was conducted in Japanese patients (treatment-naive, n = 659; bisphosphonate-pretreated, n = 774) with osteoporosis at high risk of fracture who received 24-month treatment of daily teriparatide. Bone mineral density increased significantly from baseline at 24 months in both treatment-naive (lumbar spine, 13.45%; femoral neck, 5.16%; total hip, 4.46%) and bisphosphonate-pretreated (lumbar spine, 11.20%; femoral neck, 2.22%; total hip, 0.67%) patients. The incidence rates of new vertebral and non-vertebral fractures at 24 months were

1.69% and 3.37%, respectively, in treatment-naive patients and 3.60% and 5.56%, respectively, in bisphosphonate-pretreated patients. No new safety concerns and effectiveness of teriparatide were observed in osteoporotic Japanese patients, regardless of their previous treatment status with bisphosphonates (92).

In conclusion, based on postmarketing experience with the originator product Forsteo / Forteo and medicinal products containing teriparatide, it may be assumed that the active agent under discussion is well-established in the indications claimed by the applicant.

The characteristics of teriparatide are described in the proposed SmPC for TERIPARATIDE (G1); necessary warnings, precautions and known or potential interactions are stated comprehensively.

2.5.6 Benefits and risks conclusions

The medicinal product TERIPARATIDE 20 micrograms/80 microliters solution for injection in pre-filled pen contains the peptide teriparatide. Teriparatide (PTH [1-34]) is the international non-proprietary name (INN) for the biologically active 34-amino acid N-terminal fragment of the 84-amino acid native parathyroid hormone (PTH [1-84]).

Teriparatide can be either manufactured by chemical solid phase peptide synthesis (as in the product under discussion) or produced in *Escherichia coli* using recombinant DNA technology (as in the reference product Forsteo). The clinical performance, efficacy and safety of teriparatide are irrespective of its mode of synthesis.

Endogenous PTH plays a central role in calcium and phosphate metabolism in the bone and kidneys, thereby controlling bone formation. Teriparatide binds to receptors with the same affinity as PTH and thus has the same activity as PTH. When given intermittently (i.e. once-daily at a dose of 20 µg by subcutaneous [s.c.] administration), teriparatide enhances osteoblastic rather than osteoclastic activity, thereby promoting the formation of new bone. The net effect on the human skeleton is increased trabecular bone mass and improved trabecular microarchitecture.

Teriparatide is indicated for use in adults. The indications comprise treatment of postmenopausal osteoporosis, male osteoporosis and osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture.

The majority of medications currently authorised for the treatment of osteoporosis exhibit antiresorptive activity by reducing bone turnover and inhibiting osteoclast-mediated bone loss, thereby stabilising bone mass. Antiresorptive agents (including oestrogen, bisphosphonates, raloxifene and denosumab) increase bone mineral density (BMD) but they are not associated with significant increases in bone mass and may impair bone remodelling when used long-term. In contrast, teriparatide stimulates modelling-based bone formation. Besides improving BMD, the peptide provides some remediation of architectural defects in the osteoporotic skeleton. During the first months of teriparatide treatment, a rapid rise in biochemical markers of bone formation reflects the stimulation of osteoid formation without an accompanying increase in bone resorption. Subsequently, serum levels of markers of bone turnover, for example procollagen type I N-terminal propeptide (PINP) and C-terminal cross-linking telopeptide of type I collagen (CTX), peak after 6 - 12 months of teriparatide therapy, after which these markers of both osteoblast and osteoclast activity slowly revert toward baseline levels. Teriparatide induces its largest increases in BMD at the spine, an anatomic site rich in trabecular bone. Changes in total hip and femoral neck BMD are minimal in the first year but increase modestly thereafter. Histological examinations confirmed that increases in the trabecular bone score and resistance to fracture occurred without evidence of cellular toxicity or adverse effects on bone architecture or mineralisation.

After the s.c. injection of a 20 µg-dose, teriparatide reaches peak serum concentration at about 30 min and decreases within 3 hours. The absolute bioavailability of teriparatide is about 95%. The serum distribution half-life is 5 min when administered intravenously and about one hour when administered subcutaneously. Metabolism of teriparatide occurs by non-specific enzymatic mechanisms in the liver; excretion is via the kidneys. Dosage adjustment based on age or mild to moderate renal impairment is not required but teriparatide should not be used in severe renal impairment.

In the pivotal trial, the Fracture Prevention Trial enrolling > 1600 postmenopausal women with osteoporosis, teriparatide given for a mean of 19 months significantly increased BMD of the lumbar spine and total hip by 9% and 4%, respectively, compared with placebo ($p < 0.001$). Efficacy was not influenced by age, baseline rate of bone turnover and baseline BMD. Teriparatide reduced the incidence of one or more new vertebral fractures by 65% and multiple fractures by 77%. The incidence of fragility non-vertebral fractures was reduced by 53%. The positive effects of teriparatide on BMD and the reduction of the overall fracture risk were confirmed in numerous subsequent clinical trials, both with controlled randomised or observational design, including women and men affected by osteoporosis. In patients with glucocorticoid-induced osteoporosis, teriparatide demonstrated superior BMD and fracture efficacy results compared with the bisphosphonate alendronate. Previous use of bisphosphonates does not significantly attenuate BMD gains from teriparatide therapy.

The duration of treatment with teriparatide should not exceed 24 months and further courses should not be repeated over a patient's lifetime. This requirement is due to the fact that carcinogenicity studies in rats caused a dose-dependent increase in the incidences of malignant bone tumours. However, maintenance of bone tissue is different in rodents and primates, and long-term teriparatide treatment in cynomolgus monkeys did not elicit bone tumours or any other neoplasms. While these findings provide some insurance, the mechanism of tumour formation is still not fully understood and osteosarcoma poses a potential risk. Therefore, treatment > 2 years must be avoided. To date, postmarketing surveillance did not identify incident cases of osteosarcoma in patient registries.

While the restriction to a maximum 24-month treatment period is based on safety issues, osteoporotic patients appear to benefit from the full course. Studies with follow-up periods of 18 months after drug discontinuation indicate that teriparatide continues to protect patients from fractures. Subsequent treatment with bisphosphonates or denosumab can support preservation of bone quality achieved with teriparatide. There is, however, no clear benefit to repeated or cyclical treatment. Combination treatment, particularly with denosumab, achieves greater BMD increase than either agent alone, but there are no available fracture data for combination treatment.

Observations from clinical trials and postmarketing data indicate that teriparatide is generally very well tolerated. Adverse events most commonly reported in teriparatide recipients comprise nausea, headache, pain in limb / muscle cramps, fatigue / asthenia and dizziness / vertigo, depression and dyspnoea. While calcium levels transiently increase after the application of teriparatide, they generally return to baseline before the next dose and persistent hypercalcaemia is rare. Serious adverse events are uncommon. In clinical trials, adverse events were not significantly different between groups receiving teriparatide and comparator agents, and they were mostly deemed to be unrelated to study drugs. The intrinsic immunogenicity associated with teriparatide appears to be negligible and, while anaphylaxis has been reported rarely, there is no evidence of hypersensitivity to teriparatide.

Based on the extensive bibliographic documentation, the clinical experience of teriparatide containing medicinal products worldwide and about 15 years market experience with the originator (reference) product Forsteo / Forteo, the data presented and discussed consistently demonstrate that teriparatide is an efficacious and overall well-tolerated medication when used as indicated, i.e. for treatment of osteoporosis in postmenopausal women and in osteoporotic in men as well as in sustained systemic glucocorticoid therapy in women and men at high risk for fracture, as specified in detail in the proposed SmPC (G1).

Similarity has been demonstrated of the product under discussion to the reference product. Both products have exactly the same qualitative and quantitative composition with regard to the active ingredient and the excipients. Equivalence was demonstrated for the identity, amino acid sequence and structure of teriparatide. Comparable biological activity was demonstrated and, furthermore, the impurity profile and degradation profile of both formulations were shown to be equivalent.

The known side effect profile of teriparatide as well as respective precautions and warnings are covered by the proposed SmPC of the applicant. An overall review of the findings allows the conclusion that this document comprehensively reflects the prevailing scientific knowledge on teriparatide in the indications claimed by the applicant.

In conclusion, the clinical documentation is adequate to support the granting of this application for authorisation of TERIPARATIDE 20 micrograms/80 microliters solution for injection in pre-filled pen as a medicinal product for the indications stated in the proposed SmPC.

2.5.7 References

General references (assessed August 2018, if applicable)

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