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EVFRAXY™ Denosumab 60 mg/mL Solution For Injection In Pre-Filled Syringe

NAME OF THE MEDICINAL PRODUCT

EVFRAXY™ Denosumab 60 mg/mL Solution for Injection in Pre-Filled Syringe

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 60 mg of denosumab in 1 mL of solution (60 mg/mL).
Denosumab is a human monoclonal IgG2 antibody produced in a mammalian cell line (Chinese hamster ovary cells) by recombinant DNA technology.

Excipient with known effect

This medicine contains 47 mg sorbitol in each mL of solution.

List of excipients

Acetic Acid Glacial, Sodium Acetate Trihydrate, Sodium Hydroxide, Sorbitol, Polysorbate 20, Water for Injections

PHARMACEUTICAL FORM

Solution for subcutaneous injection.
Clear to slightly opalescent, colourless to pale yellow solution.
EVFRAXY is a biosimilar product of PROLIA

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for treatment of bone diseases – Other drugs affecting bone structure and mineralisation, ATC code: M05BX04

Mechanism of action

Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL preventing RANKL from activating its only receptor, RANK, on the surface of osteoclast and their precursors, independent of bone surface. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival. Denosumab therefore, reduce bone resorption and increases bone mass and strength in both cortical and trabecular bone.

Pharmacodynamic effects

At the end of each dosing interval, CTX reductions were partially attenuated from maximal reduction of ≥ 87% to approximately ≥ 45% (range 45-80%), reflecting the reversibility of denosumab's effects
on bone remodelling once serum levels diminish. These effects were sustained with continued treatment. Bone turnover markers generally reached pre-treatment levels within 9 months after the last dose. Upon re-initiation, reductions in CTX by denosumab were similar to those observed in patients initiating primary denosumab treatment.

Immunogenicity

In clinical studies, neutralising antibodies have been detected for denosumab. Using a sensitive immunoassay < 1% of patients treated with denosumab for up to 5 years tested positive for non neutralising binding antibodies with no evidence of altered pharmacokinetics, toxicity, or clinical response.
Information below refers to Prolia

Clinical efficacy and safety in postmenopausal women with osteoporosis

Efficacy and safety of denosumab administered once every 6 months for 3 years were investigated in postmenopausal women (7,808 women aged 60-91 years, of which 23.6% had prevalent vertebral fractures) with baseline bone mineral density (BMD) T-scores at the lumbar spine or total hip between –
2.5 and –4.0 and a mean absolute 10-year fracture probability of 18.60% (deciles: 7.9-32.4%) for major osteoporotic fracture and 7.22% (deciles: 1.4-14.9%) for hip fracture. Women with other diseases or on therapies that may affect bone were excluded from this study. Women received calcium (at least 1,000 mg) and vitamin D (at least 400 IU) supplementation daily.

Effect on vertebral fractures

Denosumab significantly reduced the risk of new vertebral fractures at 1, 2 and 3 years ($p < 0.0001$) (see Table 1 below).

Table 1. The effect of denosumab on the risk of new vertebral fractures

Proportion of women with fracture (%)		Absolute risk reduction (%) (95% CI)	Relative risk reduction (%) (95% CI)	
Placebo n = 3,906			Denosumab n = 3,902	
0-1 year	2.2	0.9	1.4 (0.8, 1.9)	61 (42, 74)**
0-2 years	5.0	1.4	3.5 (2.7, 4.3)	71 (61, 79)**
0-3 years	7.2	2.3	4.8 (3.9, 5.8)	68 (59, 74)*

*p < 0.0001, **p < 0.0001 – exploratory analysis

Effect on hip fractures

Denosumab demonstrated a 40% relative reduction (0.5% absolute risk reduction) in the risk of hip fracture over 3 years ($p < 0.05$). The incidence of hip fracture was 1.2% in the placebo group compared to 0.7% in the denosumab group at 3 years.
In a post-hoc analysis in women > 75 years, a 62% relative risk reduction was observed with Denosumab (1.4% absolute risk reduction, $p < 0.01$).

Effect on all clinical fractures

Denosumab significantly reduced fractures across all fracture types/groups (see Table 2 below).

Table 2. The effect of denosumab on the risk of clinical fractures over 3 years

Proportion of women with fracture (%)+		Absolute risk reduction (%) (95% CI)	Relative risk reduction (%) (95% CI)	
Placebo n = 3,906			Denosumab n = 3,902	
Any clinical fracture1	10.2	7.2	2.9 (1.6, 4.2)	30 (19, 41)***
Clinical vertebral fracture	2.6	0.8	1.8 (1.2, 2.4)	69 (53, 80)***
Non-vertebral fracture2	8.0	6.5	1.5 (0.3, 2.7)	20 (5, 33)**
Major non-vertebral fracture3	6.4	5.2	1.2 (0.1, 2.2)	20 (3, 34)*
Major osteoporotic fracture4	8.0	5.3	2.7 (1.6, 3.9)	35 (22, 45)***

*p ≤ 0.05, **p = 0.0106 *(secondary endpoint included in multiplicity adjustment)*, ***p ≤ 0.0001
+ Event rates based on Kaplan-Meier estimates at 3 years.
1 Includes clinical vertebral fractures and non-vertebral fractures.
2 Excludes those of the vertebrae, skull, facial, mandible, metacarpus, and finger and toe phalanges.
3 Includes pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip.
4 Includes clinical vertebral, hip, forearm, and humerus fractures, as defined by the WHO.
In women with baseline femoral neck BMD ≤ -2.5, denosumab reduced the risk of non-vertebral fracture (35% relative risk reduction, 4.1% absolute risk reduction, $p < 0.001$, exploratory analysis).
The reduction in the incidence of new vertebral fractures, hip fractures and non-vertebral fractures by denosumab over 3 years were consistent regardless of the 10-year baseline fracture risk.

Effect on bone mineral density

Denosumab significantly increased BMD at all clinical sites measured, versus placebo at 1, 2 and 3 years. Denosumab increased BMD by 9.2% at the lumbar spine, 6.0% at the total hip, 4.8% at the femoral neck, 7.9% at the hip trochanter, 3.5% at the distal 1/3 radius and 4.1% at the total body over 3 years (all $p 0.0001$).
In clinical studies examining the effects of discontinuation of denosumab, BMD returned to approximately pre-treatment levels and remained above placebo within 18 months of the last dose. These data indicate that continued treatment with denosumab is required to maintain the effect of the medicinal product. Re- initiation of denosumab resulted in gains in BMD similar to those when denosumab was first administered.

Open-label extension study in the treatment of postmenopausal osteoporosis

A total of 4,550 women (2,343 denosumab & 2,207 placebo) who missed no more than one dose of investigational product in the pivotal study described above and completed the month 36 study visit agreed to enrol in a 7-year, multinational, multicentre, open-label, single-arm extension study to evaluate the long- term safety and efficacy of denosumab. All women in the extension study were to receive denosumab 60 mg every 6 months, as well as daily calcium (at least 1 g) and vitamin D (at least 400 IU). A total of 2,626 subjects (58% of the women included in the extension study i.e. 34% of the women included in the pivotal study) completed the extension study.
In patients treated with denosumab for up to 10 years, BMD increased from the pivotal study baseline by 21.7% at the lumbar spine, 9.2% at the total hip, 9.0% at the femoral neck, 13.7% at the trochanter and 2.8% at the distal 1/3 radius. The mean lumbar spine BMD T-score at the end of the study was
–1.3 in patients treated for 10 years.
Fracture incidence was evaluated as a safety endpoint but efficacy in fracture prevention cannot be estimated due to high number of discontinuations and open-label design. The cumulative incidence of new vertebral 4 and non-vertebral fractures were approximately 6.8% and 13.1% respectively, in patients who remained on denosumab treatment for 10 years (n = 1,278). Patients who did not complete the study for any reason had higher on-treatment fracture rates.
Thirteen adjudicated cases of osteonecrosis of the jaw (ONJ) and two adjudicated cases of atypical fractures of the femur occurred during the extension study.

Clinical efficacy and safety in men with osteoporosis

Efficacy and safety of denosumab once every 6 months for 1 year were investigated in 242 men aged 31- 84 years. Subjects with an eGFR < 30 mL/min/1.73 m2 were excluded from the study. All men received calcium (at least 1,000 mg) and vitamin D (at least 800 IU) supplementation daily.
The primary efficacy variable was percent change in lumbar spine BMD, fracture efficacy was not evaluated. Denosumab significantly increased BMD at all clinical sites measured, relative to placebo at 12 months: 4.8% at lumbar spine, 2.0% at total hip, 2.2% at femoral neck, 2.3% at hip trochanter, and 0.9% at distal 1/3 radius (all p < 0.05). Denosumab increased lumbar spine BMD from baseline in 94.7% of men at 1 year. Significant increases in BMD at lumbar spine, total hip, femoral neck and hip trochanter were observed by 6 months ($p < 0.0001$).

Bone histology in postmenopausal women and men with osteoporosis

Bone histology was evaluated in 62 postmenopausal women with osteoporosis or with low bone mass who were either naïve to osteoporosis therapies or had transitioned from previous alendronate therapy following 1-3 years treatment with denosumab. Fifty nine women participated in the bone biopsy sub- study at month 24 (n = 41) and/or month 84 (n = 22) of the extension study in postmenopausal women with osteoporosis. Bone histology was also evaluated in 17 men with osteoporosis following 1 year treatment with denosumab. Bone biopsy results showed bone of normal architecture and quality with no evidence of mineralisation defects, woven bone or marrow fibrosis. Histomorphometry findings in the extension study in postmenopausal women with osteoporosis showed that the antiresorptive effects of denosumab, as measured by activation frequency and bone formation rates, were maintained over time.

Clinical efficacy and safety in patients with bone loss associated with androgen deprivation

Efficacy and safety of denosumab once every 6 months for 3 years were investigated in men with histologically confirmed non-metastatic prostate cancer receiving ADT (1,468 men aged 48-97 years) who were at increased risk of fracture (defined as > 70 years, or < 70 years with a BMD T-score at the lumbar spine, total hip, or femoral neck < -1.0 or a history of an osteoporotic fracture.) All men received calcium (at least 1,000 mg) and vitamin D (at least 400 IU) supplementation daily.
Denosumab significantly increased BMD at all clinical sites measured, relative to treatment with placebo at 3 years: 7.9% at the lumbar spine, 5.7% at the total hip, 4.9% at the femoral neck, 6.9% at the hip trochanter, 6.9% at the distal 1/3 radius and 4.7% at the total body (all $p < 0.0001$). In a prospectively planned exploratory analysis, significant increases in BMD were observed at the lumbar spine, total hip, femoral neck and the hip trochanter 1 month after the initial dose.
Denosumab demonstrated a significant relative risk reduction of new vertebral fractures: 85% (1.6% absolute risk reduction) at 1 year, 69% (2.2% absolute risk reduction) at 2 years and 62% (2.4% absolute risk reduction) at 3 years (all $p < 0.01$).

Clinical efficacy and safety in patients with bone loss associated with adjuvant aromatase inhibitor therapy

Efficacy and safety of denosumab once every 6 months for 2 years were investigated in women with non- metastatic breast cancer (252 women aged 35-84 years) and baseline BMD T-scores between -1.0 to -2.5 at the lumbar spine, total hip or femoral neck. All women received calcium (at least 1,000 mg) and vitamin D (at least 400 IU) supplementation daily.
The primary efficacy variable was percent change in lumbar spine BMD, fracture efficacy was not evaluated. Denosumab significantly increased BMD at all clinical sites measured, relative to treatment with placebo at 2 years: 7.6% at lumbar spine, 4.7% at total hip, 3.6% at femoral neck, 5.9% at hip trochanter, 6.1% at distal 1/3 radius and 4.2% at total body (all $p < 0.0001$).

Treatment of bone loss associated with systemic glucocorticoid therapy

Efficacy and safety of denosumab were investigated in 795 patients (70% women and 30% men) aged 20 to 94 years treated with ≥ 7.5 mg daily oral prednisone (or equivalent).
Two subpopulations were studied: glucocorticoid-continuing (≥ 7.5 mg daily prednisone or its equivalent for ≥ 3 months prior to study enrolment; n = 505) and glucocorticoid-initiating (≥ 7.5 mg daily prednisone or its equivalent for < 3 months prior to study enrolment; n = 290). Patients were randomised (1:1) to receive either denosumab 60 mg subcutaneously once every 6 months or oral risedronate 5 mg once daily (active control) for 2 years. Patients received calcium (at least 1,000 mg) and vitamin D (at least 800 IU) supplementation daily.

Effect on Bone Mineral Density (BMD)

In the glucocorticoid-continuing subpopulation, denosumab demonstrated a greater increase in lumbar spine BMD compared to risedronate at 1 year (denosumab 3.6%, risedronate 2.0%; $p < 0.001$) and 2 years (denosumab 4.5%, risedronate 2.2%; $p < 0.001$). In the glucocorticoid-initiating subpopulation, denosumab demonstrated a greater increase in lumbar spine BMD compared to risedronate at 1 year (denosumab 3.1%, risedronate 0.8%; $p < 0.001$) and 2 years (denosumab 4.6%, risedronate 1.5%; $p < 0.001$).
In addition, denosumab demonstrated a significantly greater mean percent increase in BMD from baseline compared to risedronate at the total hip, femoral neck, and hip trochanter.
The study was not powered to show a difference in fractures. At 1 year, the subject incidence of new radiological vertebral fracture was 2.7% (denosumab) versus 3.2% (risedronate). The subject incidence of non-vertebral fracture was 4.3% (denosumab) versus 2.5% (risedronate). At 2 years, the corresponding numbers were 4.1% versus 5.8% for new radiological vertebral fractures and 5.3% versus 3.8% for non- vertebral fractures. Most of the fractures occurred in the GC-C subpopulation.

Paediatric population

A single-arm phase 3 study evaluated the efficacy, safety, and pharmacokinetics was conducted in children with osteogenesis imperfecta, aged 2 to 17 years, 52.3% male, 88.2% Caucasian. A total of 153 subjects initially received subcutaneous (SC) denosumab 1 mg/kg, up to a maximum of 60 mg, every 6 months for 36 months. Sixty subjects transitioned to every 3 months dosing.
At month 12 of every 3 months dosing, the least squares (LS) mean (standard error, SE) change from baseline in lumbar spine BMD Z-score was 1.01 (0.12).
The most common adverse events reported during every 6 months dosing were arthralgia (45.8%), pain in extremity (37.9%), back pain (32.7%), and hypercalciuria (32.0%). Hypercalcaemia was reported during every 6 months (19%) and every 3 months (36.7%) dosing. Serious adverse events of hypercalcaemia (13.3%) were reported during every 3 months dosing.
In an extension study (N = 75), serious adverse events of hypercalcaemia (18.5%) were observed during every 3 months dosing.
The studies were terminated early due to the occurrence of life-threatening events and hospitalisations due to hypercalcaemia (see ***section Dosage and method of administration***)
Information below refers to biosimilar Evfraxy. Comparative of Evfraxy to Prolia

Study B1000- NHV-01- G-01

The Phase I PK comparability study of Bmab 1000-P versus the US-licensed Prolia comprised a randomised, double-blind, two-arm, single-dose, parallel-group study in normal healthy adult participants.
Participants were stratified based on site, ethnicity (Japanese *versus* non-Japanese), body weight (55 to <60 kg for Japanese only, 60-80 kg and 61–95 kg) and gender. Sentinel dosing was used such that 2 cohorts of 2 participants (1 Bmab 1000, 1 Prolia) were dosed at least 24 hours apart and, after confirming that no safety concerns arose. Remaining participants were dosed starting from at least 24 hours later. Post dosing, all participants were followed up for 36 weeks where blood samples were collected at scheduled timepoints for PK, PD, immunogenicity, and safety laboratory assessments. The participants were observed for a 36-week period for safety monitoring. Investigational medicinal product (IMP) was administered by subcutaneous (s.c.) injection.
Following a single s.c. dose of 60 mg Bmab 1000 and of 60 mg Prolia, the mean Cmax, AUC0-t and AUC0- inf, including the partial AUCs (AUC18-85days and AUC113-253days) were comparable between the two treatments group. The tmax, Ct, and the t1/2 were comparable between the Bmab 1000 and Prolia treatment groups. The AUCext(%) was less than 1% following administration of both study treatments reflecting that the PK sampling duration considered for the study was adequate for reliable estimation of the terminal phase. Statistical analysis demonstrated PK similarity between Bmab 1000 and Prolia as the 90% CIs of geometric least squared means (GLSMs) ratio for primary PK parameters (Cmax, AUC0-t and AUC0-inf), were entirely contained within the predefined bioequivalence range of 0.8000 and 1.2500. Statistical analysis of protein- adjusted primary PK parameters (Cmax/P, AUC0-t/P and AUC0-inf/P) supported PK similarity between Bmab 1000, and Prolia as the 90% CIs of GLSMs ratio (Test/Reference) fell within the bioequivalence range of 0.8000 and 1.2500.
Pharmacodynamic parameters AUEC0-253 days and Emax were secondary endpoints, the CIs of their GMRs are not required to fulfil any equivalence limits. However, the statistical analysis demonstrated PD similarity between Bmab 1000 and Prolia as the 95% CIs of GLSMs ratio for PD parameters (AUEC0-253 days and Emax), were entirely contained within the predefined bioequivalence range of 0.8000 and 1.2500.
The incidence of ADA in the Prolia group and in the Bmab 1000 group closely matched throughout the study: the number of participants with ADA+ increased until D57 (91 [98.9%] participants in the Bmab 1000 group and 87 [93.5%] participants in the Prolia group) and was stable until D85 (91 [98.9%] participants in the Bmab 1000 group and 88 [94.6%] participants in the Prolia group). The number of positive participants then decreased until the end of study (EOS) visit, when 5 (5.4%) participants in the Bmab 1000 group and 2 (2.2%) participants in the Prolia group were positive. The evolution of ADA titers over time in both treatment groups also matched closely.
Overall, 99 (52.4%) participants experienced at least one treatment emergent AE (TEAE), and a total of 221
TEAEs were reported: 110 TEAEs in 47 (50.0%) participants in the Bmab 1000 group and 111 TEAEs in 52 (54.7%) participants in the Prolia group. No grade 3 or higher TEAEs were reported.
Most TEAEs were grade 1, with 38 participants (40.4%) experiencing grade 1 TEAEs in the Bmab 1000 group and 32 participants (33.7%) in the Prolia group. Additionally, grade 2 TEAEs were reported and in 23 participants (24.5%) in the Bmab 1000 group and in 33 participants (34.7%) in the Prolia group. The majority of the events were not related to the study drug. In the Bmab 1000 group, 85 out of 110 TEAEs, reported in 41 (43,6%) participants, were considered not related to treatment, and in the Prolia group, 98 out of 111 TEAEs, reported in 50 (52.6%) participants, were considered not related to the study drug. Incidence of treatment related adverse events were nominally higher in the Bmab1000 group than in the Prolia group; however the number of events in each PT was low. In the Bmab 1000 group, 25 out of 110TEAEs, reported in 16 (17.0%) participants were considered related to treatment, and in the Prolia group, 13 out of 111 TEAEs, in 9 (9.5%) participants, were considered related to treatment.
The type and frequency of the TEAEs were similar in the Bmab 1000 group and in the Prolia group: the most frequent SOCs, reported in at least 5% of the overall population were infections and infestations, gastrointestinal disorders, musculoskeletal and connective tissue disorders, nervous system disorders, and general disorders and administration site conditions. The most frequent PTs reported in at least 5% of the participants in either treatment group were headache, nasopharyngitis, constipation, and back pain. A pregnancy was reported in the female partner of a male participant in Bmab 1000 group. The female partner underwent spontaneous abortion. The event was considered not related to the Bmab 1000. There was no death, no serious AE (SAE), and no TEAEs leading to study discontinuation reported in study participants. No clinically relevant changes in clinical laboratory results, vital signs, or ECG parameters were reported, and no clinically relevant difference was observed between the Bmab 1000 and the Prolia groups. A few participants presented sporadic out-of-range values for some safety parameters; none being considered clinically significant by the Investigator. Mild to moderate injection site reactions were reported in both treatment groups throughout the study; most were below the threshold for TEAE notification.
Following a single s.c. dose of 60 mg Bmab 1000 and 60 mg Prolia, the concentration-time profiles were comparable. Statistical analysis demonstrated PK similarity for PK parameters (AUC0-inf, AUC0-t, and Cmax) between Bmab 1000 and the Prolia as the 90% CIs of GLSMs ratio (Test/Reference) fell within the predefined bioequivalence range of 0.8000 and 1.2500 (i.e., 80.00% and 125.00%). The partial AUC18- 85days and AUC113-253days that were characterised to depict the linear /non-linear-TMDD pathway were similar between the treatment groups. PD parameters (AUEC0-253days and Emax) were observed to be similar between the two treatment groups. The point estimates (95% CIs) of Test/Reference GLSMs ratio derived for Emax and AUEC0-253days were entirely contained within the standard bioequivalence range of 0.8000 and 1.2500. A single dose of 60 mg Bmab 1000/Prolia was safe and well tolerated in healthy subjects across the two treatment groups. The majority of the AEs were mild in severity and were considered not related to the study drugs. The incidence of ADA was observed to be similar between the two treatment arms. The results from this study complement the comparative physical and chemical characterization of Bmab 1000 and Prolia, confirming that the demonstrated analytical comparability translates into highly similar clinical exposure over time i.e. bioequivalence and highly similar pharmacodynamic behaviour of Bmab 1000 and Prolia. Seen in context this study provides additional support for the contention that Bmab 1000 qualifies as a biosimilar to Prolia

Study B1000- PMO-03- G-02

The Phase 3 Study between Bmab 1000-P and Prolia® was conducted to compare the efficacy, safety, pharmacodynamics (PD), pharmacokinetics (PK) and immunogenicity of Bmab-1000 (a biosimilar to denosumab) and denosumab (Deno) in women with post-menopausal osteoporosis (PMO). Overall, 479 women (mean age, 66.6 years) with osteoporosis [with lumbar spine (L1-L4) absolute bone mineral density (LS-BMD) and T-score ≤–2.5-≥–4.0] were randomized 1:1 to 60 mg of Bmab-1000 (n=238) or Deno (n=241) subcutaneously. Part 1 (week 0-52) was double-blind and active-controlled, comparing Bmab-1000 to Deno (two doses on day 1 and week 26). In Part 2 (week 52-78), patients initially on Bmab- 1000 continued Bmab-1000 at week 52; n=218. Patients initially randomized to Deno (n=208) were re- randomized to Bmab-1000 or Deno at week 52 (n=104 each). Part 1 evaluated the therapeutic and PD equivalence between Bmab-1000 and Deno using %change from baseline (%CfB) in LS-BMD at week 52 and area under the effect curve (AUEC) of serum C-terminal telopeptide of Type 1 collagen (sCTX) from baseline to 26 weeks. Part 2 monitored the safety of Bmab-1000 and Deno after transition from Deno to Bmab-1000 versus continuing Deno. Secondary analyses included additional efficacy, PK, safety, and immunogenicity parameters.
Equivalence was demonstrated for the primary efficacy endpoint. The confidence intervals (CIs) for the difference in least square means (LSMs) in %CfB in LS-BMD at week 52 between Bmab-1000 and Deno were contained within the predefined margins (±1.45; LSM diff:0.610, 95% CI: -0.095, 1.316). The sCTX AUEC up to 26 weeks for Bmab-1000 was similar to that observed following a single dose of Deno (geometric LSM ratio: 104.14; 95% CI: 97.76, 110.95). The secondary efficacy, PD, PK, safety, and immunogenicity results were comparable among all groups up to Week 78, including after transitioning to Bmab-1000 from Deno.
Bmab-1000 demonstrated equivalent efficacy and PD to Deno in women with PMO with similar safety, tolerability, and immunogenicity profiles. There was no effect of transition from Deno to Bmab-1000.

Pharmacokinetic properties

Absorption

Following subcutaneous administration of a 1.0 mg/kg dose, which approximates the approved 60 mg dose, exposure based on AUC was 78% as compared to intravenous administration at the same dose level. For a 60 mg subcutaneous dose, maximum serum denosumab concentrations (Cmax) of 6 mcg/mL (range 1-17 mcg/mL) occurred in 10 days (range 2-28 days).

Biotransformation

Denosumab is composed solely of amino acids and carbohydrates as native immunoglobulin and is unlikely to be eliminated via hepatic metabolic mechanisms. Its metabolism and elimination are expected to follow the immunoglobulin clearance pathways, resulting in degradation to small peptides and individual amino acids.

Elimination

After Cmax, serum levels declined with a half-life of 26 days (range 6-52 days) over a period of 3 months (range 1.5-4.5 months). Fifty-three percent (53%) of patients had no measurable amounts of denosumab detected at 6 months post-dose.
No accumulation or change in denosumab pharmacokinetics with time was observed upon subcutaneous multiple-dosing of 60 mg once every 6 months. Denosumab pharmacokinetics were not affected by the formation of binding antibodies to denosumab and were similar in men and women. Age (28-87 years), race and disease state (low bone mass or osteoporosis; prostate or breast cancer) do not appear to significantly affect the pharmacokinetics of denosumab.
A trend was observed between higher body weight and lower exposure based on AUC and Cmax. However, the trend is not considered clinically important, since pharmacodynamic effects based on bone turnover markers and BMD increases were consistent across a wide range of body weight.

Linearity/non-linearity

In dose ranging studies, denosumab exhibited non-linear, dose-dependent pharmacokinetics, with lower clearance at higher doses or concentrations, but approximately dose-proportional increases in exposures for doses of 60 mg and greater.

Renal impairment

In a study of 55 patients with varying degrees of renal function, including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics of denosumab.

Hepatic impairment

The safety and efficacy of Evfraxy™ have not been studied in patients with hepatic impairment (see section Pharmacokinetic properties).

Paediatric population

Evfraxy™ should not be used in paediatric populations ***(see section Dosage and Method of Administration and section Pharmacodynamic Properties).***
In a phase 3 study of paediatric patients with osteogenesis imperfecta (N = 153), maximum serum denosumab concentrations were observed on day 10 across all age groups. For every 3 months and every 6 months dosing, mean serum denosumab trough concentrations were observed to be higher for children 11 to 17 years of age, while children 2 to 6 years of age had the lowest mean trough concentrations.

Preclinical safety data

In single and repeated dose toxicity studies in cynomolgus monkeys, denosumab doses resulting in 100 to 150 times greater systemic exposure than the recommended human dose had no impact on cardiovascular physiology, male or female fertility, or produced specific target organ toxicity.
Standard tests to investigate the genotoxicity potential of denosumab have not been evaluated, since such tests are not relevant for this molecule. However, due to its character it is unlikely that denosumab has any potential for genotoxicity.
The carcinogenic potential of denosumab has not been evaluated in long-term animal studies.
In preclinical studies conducted in knockout mice lacking RANK or RANKL, impairment of lymph node formation was observed in the foetus. An absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development during pregnancy) was also observed in knockout mice lacking RANK or RANKL.
In a study of cynomolgus monkeys dosed with denosumab during the period equivalent to the first trimester at AUC exposures up to 99-fold higher than the human dose (60 mg every 6 months), there was no evidence of maternal or foetal harm. In this study, foetal lymph nodes were not examined. In another study of cynomolgus monkeys dosed with denosumab throughout pregnancy at AUC exposures 119-fold higher than the human dose (60 mg every 6 months), there were increased stillbirths and postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced haematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth. A no observed adverse effect level for reproductive effects was not established. Following a 6 month period after birth, bone related changes showed recovery and there was no effect on tooth eruption. However, the effects on lymph nodes and tooth malalignment persisted, and minimal to moderate mineralisation in multiple tissues was seen in one animal (relation to treatment uncertain). There was no evidence of maternal harm prior to labour; adverse maternal effects occurred infrequently during labour. Maternal mammary gland development was normal.
In preclinical bone quality studies in monkeys on long-term denosumab treatment, decreases in bone turnover were associated with improvement in bone strength and normal bone histology. Calcium levels were transiently decreased and parathyroid hormone levels transiently increased in ovariectomised monkeys treated with denosumab.
In male mice genetically engineered to express huRANKL (knock-in mice), which were subjected to a transcortical fracture, denosumab delayed the removal of cartilage and remodelling of the fracture callus compared to control, but biomechanical strength was not adversely affected.
Knockout mice ***(see section Fertility, Pregnancy and Lactation)*** lacking RANK or RANKL exhibited decreased body weight, reduced bone growth and lack of tooth eruption. In neonatal rats, inhibition of RANKL (target of denosumab therapy) with high doses of a construct of osteoprotegerin bound to Fc (OPG- Fc) was associated with inhibition of bone growth and tooth eruption. These changes were partially reversible in this model when dosing with RANKL inhibitors was discontinued. Adolescent primates dosed with denosumab at 27 and 150 times (10 and 50 mg/kg dose) the clinical exposure had abnormal growth plates. Therefore, treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition.

CLINICAL PARTICULARS

Therapeutic indications

Postmenopausal osteoporosis
Evfraxy™ is indicated for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. In postmenopausal women with osteoporosis, Evfraxy™ increases bone mineral density (BMD) and reduces the incidence of hip, vertebral and non-vertebral fractures.
Bone loss in patients undergoing hormone ablation for cancer
Evfraxy™ is indicated for the treatment of bone loss in patients undergoing hormone ablation for prostate or aromatase inhibitor treatment for breast cancer. In patients with prostate cancer, Evfraxy™ reduces the incidence of vertebral fractures.
Male osteoporosis
Evfraxy™ is indicated as a treatment to increase bone mass in men with osteoporosis at increased risk of fracture.
Glucocorticoid-induced osteoporosis
Treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months.

Dosage and Method of administration

The recommended dose of Evfraxy™ is a single subcutaneous injection of 60 mg administered once every 6 months.
Patients should receive calcium and vitamin D supplements whilst undergoing treatment.

Populations Elderly (age ≥ 65)

No dose adjustment is required in elderly patients.

Renal impairment

No dose adjustment is required in patients with renal impairment (***see section Special warnings and precautions for use*** for recommendations relating to monitoring of calcium).
No data is available in patients with long-term systemic glucocorticoid therapy and severe renal impairment (GFR < 30 mL/min).

Hepatic impairment

The safety and efficacy of Denosumab have not been studied in patients with hepatic impairment ***(see section Pharmacokinetic properties).***

Paediatric population

Evfraxy™ should not be used in children aged < 18 years because of safety concerns of serious hypercalcaemia, and potential inhibition of bone growth and lack of tooth eruption ***(see sections Special warnings and precautions for use and Preclinical safety data).*** Currently available data for children aged 2 to 17 years are described in sections Pharmacodynamic properties and Pharmacokinetic properties.

Method of administration

For subcutaneous use.
Administration should be performed by an individual who has been adequately trained in injection techniques.
The instructions for use, handling and disposal are given in ***section Special Precautions for Disposal and Other Handling.***

Contraindications

Hypocalcaemia ***(see section Special Warnings and Precautions for Use).***
Hypersensitivity to the active substance or to any of the excipients listed in ***(see section Qualitative and Quantitative Composition).***

Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Calcium and vitamin D supplementation

Adequate intake of calcium and vitamin D is important in all patients.

Precautions for use

Hypocalcaemia

It is important to identify patients at risk for hypocalcaemia. Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Clinical monitoring of calcium levels is recommended before each dose and, in patients predisposed to hypocalcaemia within two weeks after the initial dose. If any patient presents with suspected symptoms of hypocalcaemia during treatment ***(see section Undesirable Effects*** for symptoms*)* calcium levels should be measured. Patients should be encouraged to report symptoms indicative of hypocalcaemia.
In the post-marketing setting, severe symptomatic hypocalcaemia (resulting in hospitalisation, life- threatening events, and fatal cases) has been reported.
Concomitant glucocorticoid treatment is an additional risk factor for hypocalcaemia.

Renal impairment

Patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis are at greater risk of developing hypocalcaemia. The risks of developing hypocalcaemia and accompanying parathyroid hormone elevations increase with increasing degree of renal impairment. Severe and fatal cases have been reported. Adequate intake of calcium, vitamin D and regular monitoring of calcium is especially important in these patients, see above.

Skin infections

Patients receiving denosumab may develop skin infections (predominantly cellulitis) leading to hospitalisation ***(see section Undesirable Effects)***. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.

Osteonecrosis of the jaw (ONJ)

ONJ has been reported rarely in patients receiving denosumab for osteoporosis ***(see section Undesirable Effects)***.
The start of treatment/new treatment course should be delayed in patients with unhealed open soft tissue lesions in the mouth. A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with denosumab in patients with concomitant risk factors.
The following risk factors should be considered when evaluating a patient's risk of developing ONJ:

- Potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy.
- Cancer, co-morbid conditions (e.g. Anaemia, coagulopathies, infection), smoking.
- Concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck.
- Poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures (e.g. tooth extractions).

All patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling or non-healing of sores or discharge during treatment with denosumab. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to denosumab administration.
The management plan of the patients who develop ONJ should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in ONJ. Temporary interruption of treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Osteonecrosis of the external auditory canal

5 5 5

Osteonecrosis of the external auditory canal has been reported with denosumab. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving denosumab who present with ear symptoms including chronic ear infections.

Atypical fractures of the femur Atypical femoral

Fractures have been reported in patients receiving denosumab ***(see section Undesirable Effects)***. Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur. Specific radiographic findings characterise these events. Atypical femoral fractures have also been reported in patients with certain co-morbid conditions (e.g. vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of certain medicinal products (e.g. bisphosphonates, glucocorticoids, proton pump inhibitors). These events have also occurred without antiresorptive therapy. Similar fractures reported in association with bisphosphonates are often bilateral; therefore, the contralateral femur should be examined in denosumab-treated patients who have sustained a femoral shaft fracture. Discontinuation of Evfraxy™ therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient based on an individual benefit-risk assessment. During Evfraxy™ treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Patients presenting with such symptoms should be evaluated for an incomplete femoral fracture.

Long-term antiresorptive treatment

Long-term antiresorptive treatment (including both denosumab and bisphosphonates) may contribute to an increased risk for adverse outcomes such as osteonecrosis of the jaw and atypical femur fractures due to significant suppression of bone remodelling ***(see section Dosage and method of administration)***.

Concomitant treatment with other denosumab-containing medicinal products

Patients being treated with Evfraxy™ should not be treated concomitantly with other denosumab- containing medicinal products (for prevention of skeletal related events in adults with bone metastases from solid tumours).

Hypercalcaemia in paediatric patients

Evfraxy™ should not be used in paediatric patients (age < 18). Serious hypercalcaemia has been reported. Some clinical trial cases were complicated by acute renal injury.

Multiple vertebral fractures (MVF) following discontinuation of denosumab treatment

Multiple vertebral fractures (MVF) may occur following discontinuation of treatment with denosumab,

particularly in patients with a history of vertebral fracture. Advise patients not to interrupt denosumab therapy without their physician's advice. Evaluate the individual benefit/risk before discontinuing treatment with denosumab. If denosumab treatment is discontinued, consider transitioning to an alternative antiresorptive therapy.

Warnings for excipients

This medicine contains 47 mg sorbitol in each mL of solution. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

This medicinal product contains less than 1 mmol sodium (23 mg) per 60 mg that is to say essentially 'sodium-free'.

Interaction with other medicaments

In an interaction study, denosumab did not affect the pharmacokinetics of midazolam, which is metabolised by cytochrome P450 3A4 (CYP3A4). This indicates that denosumab should not alter the pharmacokinetics of medicinal products metabolised by CYP3A4.

There are no clinical data on the co-administration of denosumab and hormone replacement therapy (oestrogen), however the potential for a pharmacodynamic interaction is considered to be low.

In postmenopausal women with osteoporosis the pharmacokinetics and pharmacodynamics of denosumab were not altered by previous alendronate therapy, based on data from a transition study (alendronate to denosumab).

Fertility, pregnancy and lactation Pregnancy

There are no or limited amount of data from the use of denosumab in pregnant women. Studies in animals have shown reproductive toxicity ***(see section Preclinical Safety Data)***.

Evfraxy™ is not recommended for use in pregnant women and women of child-bearing potential not using contraception. Women should be advised not to become pregnant during and for at least 5 months after treatment with Evfraxy™. Any effects of Evfraxy™ are likely to be greater during the second and third trimesters of pregnancy since monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Breast-feeding

It is unknown whether denosumab is excreted in human milk. In genetically engineered mice in which RANKL has been turned off by gene removal (a "knockout mouse"), studies suggest absence of RANKL (the target of denosumab ***see section Pharmacodynamic Properties***) during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum ***(see section Preclinical Safety Data)***. A decision on whether to abstain from breast-feeding or to abstain from therapy with Evfraxy™ should be made, taking into account the benefit of breast-feeding to the newborn/infant and the benefit of Evfraxy™ therapy to the woman

Fertility

No data are available on the effect of denosumab on human fertility. Animal studies do not indicate direct or indirect harmful effects with respect to fertility ***(see section Preclinical Safety Data)***.

Undesirable effects

Summary of the safety profile

The most common side effects with denosumab (seen in more than one patient in ten) are musculoskeletal pain and pain in the extremity. Uncommon cases of cellulitis, rare cases of hypocalcaemia, hypersensitivity, osteonecrosis of the jaw and atypical femoral fractures ***(see sections Special Warnings and Precautions for Use and section Undesirable Effects*** - description of selected adverse reactions) have been observed in patients taking denosumab.

Tabulated list of adverse reactions

The data in table below describe adverse reactions reported from phase II and III clinical trials in patients with osteoporosis and breast or prostate cancer patients receiving hormone ablation; and/or spontaneous reporting.

The following convention has been used for the classification of the adverse reactions (see Table 3): very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and not known (cannot be estimated from the available data). Within each frequency grouping and system organ class, adverse reactions are presented in order of decreasing seriousness.

Table 3. Adverse reactions reported in patients with osteoporosis and breast or prostate cancer patients receiving hormone ablation

MedDRA system organ class	Frequency category	Adverse reactions
Infections and infestations	Common	Urinary tract infection
Common		Upper respiratory tract infection
Uncommon		Diverticulitis1
Uncommon		Cellulitis1
Uncommon		Ear infection
Immune system disorders	Rare	Drug hypersensitivity1
Rare		Anaphylactic reaction1
Metabolism and nutrition disorders	Rare	Hypocalcaemia1
Nervous system disorders	Common	Sciatica
MedDRA system organ class	**Frequency category**	**Adverse reactions**
Gastrointestinal disorders	Common	Constipation
Common		Abdominal discomfort
Skin and subcutaneous tissue disorders	Common	Rash
Common		Eczema
Common		Alopecia
Uncommon		Lichenoid drug eruptions1
Very rare Not known		Hypersensitivity vasculitis Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome
Musculoskeletal and connective tissue disorders	Very common	Pain in extremity
Very common		Musculoskeletal pain1
Uncommon Rare		Multiple vertebral fractures1,2 Osteonecrosis of the jaw1
Rare		Atypical femoral fractures1
Not Known		Osteonecrosis of the external auditory canal3

1 See ***section Description*** of selected adverse reactions.

2 Adverse reaction observed following discontinuation of treatment with Denosumab

3 See ***section Special Warnings and Precautions for Use***.

In a pooled analysis of data from all phase II and phase III placebo-controlled studies, influenza-like illness was reported with a crude incidence rate of 1.2% for denosumab and 0.7% for placebo.

Although this imbalance was identified via a pooled analysis, it was not identified via a stratified analysis.

Description of selected adverse reactions

Hypocalcaemia

In two phase III placebo-controlled clinical trials in postmenopausal women with osteoporosis, approximately 0.05% (2 out of 4,050) of patients had declines of serum calcium levels (less than 1.88 mmol/L) following denosumab administration. Declines of serum calcium levels (less than 1.88 mmol/L) were not reported in either the two phase III placebo-controlled clinical trials in patients receiving hormone ablation or the phase III placebo-controlled clinical trial in men with osteoporosis.

In the post-marketing setting, rare cases of severe symptomatic hypocalcaemia have been reported predominantly in patients at increased risk of hypocalcaemia receiving denosumab, with most cases occurring in the first weeks of initiating therapy. Examples of the clinical manifestations of severe symptomatic hypocalcaemia have included QT interval prolongation, tetany, seizures and altered mental status ***(see section Special Warnings and Precautions for Use)***. Symptoms of hypocalcaemia in denosumab clinical studies included paraesthesias or muscle stiffness, twitching, spasms and muscle cramps.

Skin infections

In phase III placebo-controlled clinical trials, the overall incidence of skin infections was similar in the placebo and the denosumab groups: in postmenopausal women with osteoporosis (placebo [1.2%, 50 out of 4,041] versus denosumab [1.5%, 59 out of 4,050]); in men with osteoporosis (placebo [0.8%, 1 out of 120] versus denosumab [0%, 0 out of 120]); in breast or prostate cancer patients receiving hormone ablation (placebo [1.7%, 14 out of 845] versus denosumab [1.4%, 12 out of 860]). Skin infections leading to hospitalisation were reported in 0.1% (3 out of 4,041) of postmenopausal women with osteoporosis receiving placebo versus 0.4% (16 out of 4,050) of women receiving denosumab.

These cases were predominantly cellulitis. Skin infections reported as serious adverse reactions were similar in the placebo (0.6%, 5 out of 845) and the denosumab (0.6%, 5 out of 860) groups in the breast and prostate cancer studies.

Osteonecrosis of the jaw

ONJ has been reported rarely, in 16 patients, in clinical trials in osteoporosis and in breast or prostate cancer patients receiving hormone ablation including a total of 23,148 patients ***(see section Special Warnings and Precautions for Use)***.

Thirteen of these ONJ cases occurred in postmenopausal women with osteoporosis during the phase III clinical trial extension following treatment with denosumab for up to 10 years. Incidence of ONJ was 0.04% at 3 years, 0.08% at 5 years and 0.44% at 10 years of denosumab treatment. The risk of ONJ increased with duration of exposure to denosumab.

Atypical fractures of the femur

In the osteoporosis clinical trial program, atypical femoral fractures were reported rarely in patients treated with denosumab ***(see section Special Warnings and Precautions for Use)***.

Diverticulitis

In a single phase III placebo-controlled clinical trial in patients with prostate cancer receiving androgen deprivation therapy (ADT), an imbalance in diverticulitis adverse events was observed (1.2% denosumab, 0% placebo). The incidence of diverticulitis was comparable between treatment groups in postmenopausal women or men with osteoporosis and in women undergoing aromatase inhibitor therapy for non-metastatic breast cancer.

Drug-related hypersensitivity reactions

In the post-marketing setting, rare events of drug-related hypersensitivity, including rash, urticaria, facial swelling, erythema, and anaphylactic reactions have been reported in patients receiving denosumab.

Musculoskeletal pain

Musculoskeletal pain, including severe cases, has been reported in patients receiving denosumab in the post- marketing setting. In clinical trials, musculoskeletal pain was very common in both denosumab and placebo groups. Musculoskeletal pain leading to discontinuation of study treatment was uncommon.

Multiple Vertebral Fractures following discontinuation of Denosumab treatment

In the osteoporosis clinical trial program, MVF were reported uncommonly in patients following discontinuation of treatment with denosumab, particularly in those with a history of vertebral fracture.

Lichenoid drug eruptions

Lichenoid drug eruptions (e.g. lichen planus-like reactions) have been reported in patients in the post- marketing setting.

Other special populations

Paediatric population

Evfraxy™ should not be used in paediatric patients (age < 18). Serious hypercalcaemia has been reported ***(see section Pharmacodynamic Properties)***. Some clinical trial cases were complicated by acute renal injury.

Renal impairment

In clinical studies, patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis were at greater risk of developing hypocalcaemia in the absence of calcium supplementation. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis ***(see section Special Warnings and Precautions for Use)***.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions as per local regulations.

Overdose

There is no experience with overdose in clinical studies. Denosumab has been administered in clinical studies using doses up to 180 mg every 4 weeks (cumulative doses up to 1,080 mg over 6 months), and no additional adverse reactions were observed.

Effects on ability to drive and use machines

Evfraxy™ has no or negligible influence on the ability to drive and use machines.

Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.

Once removed from the refrigerator, Evfraxy™ may be stored at room temperature (up to 25°C) for up to 30 days in the original carton. It must be used within this 30 days period.

Shelf life

Refer to Carton/Label.

Nature and contents of container

One mL solution in a single use pre-filled syringe made from type I glass with stainless steel needle (29 G×½-inch), with needle guard.

Pack size of one pre-filled syringe, presented in blistered packaging (pre-filled syringe with a needle guard)

Instruction for Use

Special precautions for disposal and other handling

- Before administration, the solution should be inspected. Do not inject the solution if it contains particles, or is cloudy or discoloured.
- Do not shake.
- To avoid discomfort at the site of injection, allow the pre-filled syringe to reach room temperature (up to 25°C) before injecting and inject slowly.
- Inject the entire contents of the pre-filled syringe.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Instructions for use:

Guide to Parts

Before Usage	After Usage

Figure A

Important Information

Read the Patient Information for important information you need to know about Evfraxy™ before using these Instructions for Use

Before you use a Evfraxy™ pre-filled syringe with automatic needle safety guard, read this important information:

- It is important that you do not try to give yourself the injection unless you have received training from your doctor or healthcare provider.
- The prefilled syringe has a needle safety guard that will be activated to cover the needle after the injection is given. The needle guard will help prevent needle stick injuries to anyone who handles the prefilled syringe after the injection has been given.
- Make sure that the name **Evfraxy™** appears on the carton and pre-filled syringe label.
- **Evfraxy™** is given as an injection into the tissue just under the skin (subcutaneous injection).

X **Do not** use the prefilled syringe if the carton is open or damaged.

X **Do not** remove the grey needle cap from the pre-filled syringe until you are ready to inject.

X **Do not** use the pre-filled syringe if it has been dropped on a hard surface. Use a new pre-filled syringe and call your doctor or healthcare provider

X **Do not** attempt to activate the pre-filled syringe prior to injection

X **Do not** attempt to remove the clear pre-filled syringe safety guard from the pre-filled syringe

X **Do not** use the pre-filled syringe if broken, preactivated or dismantled from the needle guard Call your doctor or healthcare provider if you have any questions.

Storing the Evfraxy™ prefilled syringe

- Store **Evfraxy™** in a refrigerator at 2°C to 8°C in the original carton.
- **Do not** freeze. Prior to administration, **Evfraxy™** may be allowed to reach room temperature (up to 25°C) in the original container.
- Once removed from the refrigerator, **Evfraxy™** must not be exposed to temperatures above 25°C and must be used within 30 days. If not used within the 30 days, **Evfraxy™** should be discarded. See **Step 4: Disposing of used prefilled syringes.**

Step 1: **Gather Supplies**

- Find a clean, well-lit and flat work surface.
- Take the prefilled syringe carton out of the refrigerator and place it on your clean work surface. Allow it to reach room temperature for 30 minutes before giving an injection.
- Remove the prefilled syringe tray from the carton.
- Wash your hands thoroughly with soap and water.
- Gather the supplies needed for your injection (not included)

Figure B: alcohol wipes

- cotton ball or gauze pad
- plaster
- sharps disposal container

Figure B

x **Do not** try to warm the syringe by using a heat source such as hot water or microwave.

x **Do not** leave the pre-filled syringe exposed to direct sunlight.

x **Do not** shake the pre-filled syringe.

- Keep the pre-filled syringe out of the sight and reach of children.

Step 2: **Prepare for injection**

- Open the tray by peeling away the cover. Grab the pre-filled syringe safety guard to remove the pre- filled syringe from the tray (**Figure C**).

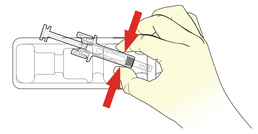


Figure C

For safety reasons:

x **Do not grasp the plunger.**

x **Do not grasp the grey needle cap.**

- Inspect the medicine and pre-filled syringe (Figure D).

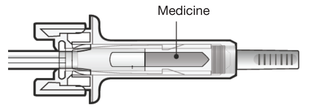


Figure D

X Do not use the pre-filled syringe if:

- The medicine is cloudy or there are particles in it. It must be a clear to slightly opalescent, colorless to pale yellow solution.
- Any part appears cracked or broken.
- The grey needle cap is missing or not securely attached.
- The expiry date printed on the label has passed the last day of the month shown.

In all cases, use new pre-filled syringe and call your doctor or healthcare provider.

- Wash your hands thoroughly. Prepare and clean your injection site.

You can use (Figure E):

- Upper part of your thigh.
- Belly, except for a 5 cm (2-inch) area right around your belly button.
- Outer area of upper arm (only if someone else is giving you the injection).

Figure E

Clean the injection site with an alcohol wipe. Let your skin dry.

X **Do not** touch the injection site before injecting.

X **Do not** inject into areas where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.

- Hold the prefilled syringe by the needle safety guard. When ready, carefully pull the grey needle cap straight off and away from the body (Figure F).

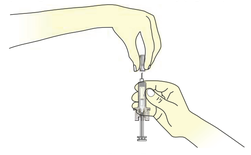


Figure F

X Do not twist or bend the gray needle cap.

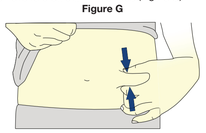
X Do not hold the pre-filled syringe by the plunger rod

- Throw the grey needle cap into the disposal container

Step 3: **Prepare for injection**

- Pinch your injection site to create a firm surface (Figure G).

Figure G



! It is important to keep the skin pinched when injecting

- Hold the pinch. INSERT the needle into skin (Figure H).

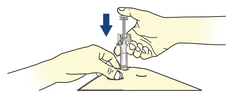


Figure H

X **Do not** touch the cleaned area of the skin.

- PUSH the plunger with slow and constant pressure until you feel or hear a "snap". Push all the way down through the snap (Figure I).

Figure I

- ! It is important to push down through the "snap" to deliver your full dose.
- Once the entire dose has been injected, the needle safety guard will be triggered. You can do either of the following: (Refer Figure J).
- Release the plunger until the entire needle is covered and then remove the needle from the injection site.

Or

- Gently remove the needle from the injection site and release the plunger until the entire needle is covered by the needle safety guard.

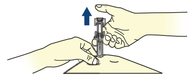


Figure J

After releasing the plunger, the pre-filled syringe safety guard will safely cover the injection needle.

- If the needle safety guard is not activated or only partially activated, discard the product (without replacing the needle cap). See "Step 4: Disposing of used prefilled syringes".

X **Do not** put the grey needle cap back on used pre-filled syringes.

- Examine the injection site.

If there is blood, press a cotton ball or gauze pad on your injection site. **Do not** rub the injection site. Apply a plaster if needed.

Step 4: **Disposing of used prefilled syringes**

- Discard the used pre-filled syringe and other supplies in a sharps disposal container (Figure K).

Figure K

Medicines should be disposed of in accordance with local requirements. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Keep the used syringe and sharps disposal container out of sight and reach of children.

X **Do not** reuse the pre-filled syringe.

X **Do not** recycle pre-filled syringes or throw them into household waste.

1. Product Registration Holder:
Biocon Sdn. Bhd.
No. 1, Jalan Bioteknologi 1, Kawasan Perindustrian SiLC, 79200, Iskandar Puteri, Johor, Malaysia.

2. Manufacturer & Batch Releaser:
Biocon Biologics Limited
Block No. B1, B2, B3, Q13 of Q1 and W20 & Unit S18, 1st Floor, Block B4, Special Economic Zone,
Plot No. 2, 3, 4 & 5, Phase IV Bommasandra-Jigani Link Road, Bommasandra, Bengaluru - 560099, India.

3. Importer & Distributor:
Duopharma HAPI Sdn. Bhd.
No. 2, Jalan Saudagar U1/16, Pusat Perindustrian Hicom Glenmarie, Seksyen U1, 40150 Shah Alam, Selangor, Malaysia

4. Date of Revision: April 2026

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