SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

EVENITY 105 mg solution for injection in pre-filled pen
EVENITY 105 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

EVENITY 105 mg solution for injection in pre-filled pen

Each pre-filled pen contains 105 mg of romosozumab in 1.17 ml of solution (90 mg/ml).

EVENITY 105 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 105 mg of romosozumab in 1.17 ml of solution (90 mg/ml).

Romosozumab is a humanized IgG2 monoclonal antibody produced using recombinant DNA technology in Chinese hamster ovary (CHO) cells.

Excipients with known effect

Each pre-filled pen and each pre-filled syringe contains 0.07 mg polysorbate 20.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

Clear to opalescent, colorless to light yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EVENITY is indicated in treatment of severe osteoporosis in postmenopausal women at high risk of fracture (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated and supervised by specialist physicians experienced in the management of osteoporosis.

Posology

The recommended dose is 210 mg romosozumab (administered as two subcutaneous injections of 105 mg each) once monthly for 12 months.

Patients should be adequately supplemented with calcium and vitamin D before and during treatment (see sections 4.3 and 4.4).

Patients treated with EVENITY should be given the package leaflet and the patient alert card.

Following completion of romosozumab therapy, transition to antiresorptive therapy is recommended in order to extend the benefit achieved with romosozumab beyond 12 months.

Missed doses
If the romosozumab dose is missed, it should be administered as soon as it can be feasible. Thereafter, the next romosozumab dose should not be given earlier than one month after the last dose.

Special populations

Elderly
No dose adjustment is necessary in elderly patients (see also section 5.2).

Renal impairment
No dose adjustment is required in patients with renal impairment (see section 5.2). Serum calcium should be monitored in patients with severe renal impairment or receiving dialysis (see section 4.4).

Hepatic impairment
No clinical trials have been conducted to evaluate the effect of hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of romosozumab in paediatric patients (age <18 years) have not yet been established. No data are available.

Method of administration

Subcutaneous use
To administer the 210 mg dose, 2 subcutaneous injections of romosozumab should be given into the abdomen, thigh, or upper arm. The second injection should be given immediately after the first one, but at a different injection site.

Administration should be performed by an individual who has been trained in injection techniques.

For instructions on handling and disposal see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see section 4.4)
- Hypocalcaemia (see section 4.4)
- History of myocardial infarction or stroke (see section 4.4)

4.4 Special warnings and precautions for use

Myocardial infarction and stroke

In randomised controlled studies, an increase in serious cardiovascular events (myocardial infarction and stroke) has been observed in romosozumab treated patients compared to controls (see section 4.8).

Romosozumab is contraindicated in patients with previous myocardial infarction or stroke (see section 4.3).

When determining whether to use romosozumab for an individual patient, consideration should be given to her fracture risk over the next year and her cardiovascular risk based on risk factors (e.g. established cardiovascular disease, hypertension, hyperlipidaemia, diabetes mellitus, smoking, severe renal impairment, age). Romosozumab should only be used if the prescriber and patient agree that the benefit outweighs the risk. If a patient experiences a myocardial infarction or stroke during therapy, treatment with romosozumab should be discontinued.

Hypocalcaemia

Transient hypocalcaemia has been observed in patients receiving romosozumab.
Hypocalcaemia should be corrected prior to initiating therapy with romosozumab and patients should be monitored for signs and symptoms of hypocalcaemia. If any patient presents with suspected symptoms of hypocalcaemia during treatment (see section 4.8), calcium levels should be measured. Patients should be adequately supplemented with calcium and vitamin D (see sections 4.3 and 4.8).

Patients with severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 29 ml/min/1.73 m^2) or receiving dialysis are at greater risk of developing hypocalcaemia and the safety data for these patients is limited. Calcium levels should be monitored in these patients.

Hypersensitivity

Clinically significant hypersensitivity reactions, including angioedema, erythema multiforme, and urticaria occurred in the romosozumab group in clinical trials. If an anaphylactic or other clinically significant allergic reaction occurs, appropriate therapy should be initiated and use of romosozumab should be discontinued (see sections 4.3 and 4.8).

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ), has been reported rarely in patients receiving romosozumab. 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 (the risk increases with the antiresorptive potency of the compound), and cumulative dose of antiresorptive 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 romosozumab.

Patients who are suspected of having or who develop ONJ while on romosozumab should receive care by a dentist or an oral surgeon with expertise in ONJ. Discontinuation of romosozumab therapy should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Atypical femoral fractures

Atypical low-energy or low trauma fracture of the femoral shaft, which can occur spontaneously, has been reported rarely in patients receiving romosozumab. Any patient who presents with new or unusual thigh, hip, or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patient presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of romosozumab therapy should be considered, based on an individual benefit-risk assessment.

Excipients

This medicine contains 0.070 mg of polysorbate 20 in each pre-filled pen and each pre-filled syringe. Polysorbates may cause allergic reactions.

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

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been performed with romosozumab. No pharmacokinetic drug interactions are expected with romosozumab.

4.6 Fertility, pregnancy and lactation

Pregnancy

Romosozumab is not indicated for use in women of child-bearing potential or in pregnant women. There are no data from the use of romosozumab in pregnant women. Skeletal malformations (including syndactyly and polydactyly) were observed at a low incidence in a single study with romosozumab in rats (see section 5.3). A risk for malformations of developing digits in the human foetus is low following romosozumab exposure due to the timing of digit formation in the first trimester in humans, a period when placental transfer of immunoglobulins is limited.

Breast-feeding

Romosozumab is not indicated for use in breast-feeding women.

No data are available on excretion of romosozumab in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period.

Fertility

No data are available on the effect of romosozumab on human fertility. Animal studies in female and male rats did not show any effects on fertility endpoints (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions were nasopharyngitis (13.6%) and arthralgia (12.4%). Hypersensitivity-related reactions occurred in 6.7% of patients treated with romosozumab. Hypocalcaemia was reported uncommonly (0.4% of patients treated with romosozumab). In randomised controlled studies, an increase in serious cardiovascular events (myocardial infarction and stroke) has been observed in romosozumab treated patients compared to controls (see section 4.4 and information below).

Tabulated list of adverse reactions

The following convention has been used for the classification of the adverse reactions:
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) and very rare (< 1/10,000). Within each frequency grouping and system organ class, adverse reactions are presented in order of decreasing seriousness.

MedDRA System Organ Class	Adverse reaction	Frequency category
Infections and infestations	Nasopharyngitis Sinusitis	Very common Common
Immune system disorders	Hypersensitivity[a] Rash Dermatitis Urticaria Angioedema Erythema multiforme	Common Common Common Uncommon Rare Rare
Metabolism and nutrition disorders	Hypocalcaemia[b]	Uncommon
Nervous system disorders	Headache Stroke[c]	Common Uncommon
Eye disorders	Cataract	Uncommon
Cardiac disorders	Myocardial infarction[c]	Uncommon
Musculoskeletal and connective tissue disorders	Arthralgia Neck pain Muscle spasms	Very common Common Common
General disorders and administration site conditions	Injection site reactions[d]	Common

a. See sections 4.3 and 4.4.
b. Defined as albumin adjusted serum calcium that was below the lower limit of normal. See sections 4.3 and 4.4.
c. See section "Myocardial infarction and stroke" below.
d. Most frequent injection site reactions were pain and erythema.

Description of selected adverse reactions

Immunogenicity
In postmenopausal women dosed with monthly romosozumab, the incidence of anti-romosozumab antibodies was 18.6% (1162 of 6244) for binding antibodies and 0.9% (58 of 6244) for neutralizing antibodies. The earliest onset of anti-romosozumab antibodies was 3 months after first dosing. The majority of antibody responses were transient.
The presence of anti-romosozumab binding antibodies decreased romosozumab exposure by up to 25%. No impact on the efficacy of romosozumab was observed in the presence of antiromosozumab antibodies. Limited safety data show that the incidence of injection site reactions was numerically higher in female patients with neutralizing antibodies.

Myocardial infarction, stroke and mortality
In the active-controlled trial of romosozumab for the treatment of severe osteoporosis in postmenopausal women during the 12-month double-blind romosozumab treatment phase, 16 women (0.8%) had myocardial infarction in the romosozumab arm versus 5 women (0.2%) in the alendronate arm and 13 women (0.6%) had stroke in the romosozumab arm versus 7 women (0.3%) in the alendronate arm. These events occurred in patients with and without a history of myocardial infarction or stroke. Cardiovascular death occurred in 17 women (0.8%) in the romosozumab group and 12 (0.6%) women in the alendronate group. The number of women with major adverse cardiac events (MACE = positively adjudicated cardiovascular death, myocardial infarction or stroke) was 41 (2.0%) in the romosozumab group and 22 (1.1%) in the alendronate group, yielding a hazard ratio of 1.87 (95% confidence interval [1.11, 3.14]) for romosozumab compared to alendronate. All-cause death occurred in 30 women (1.5%) in the romosozumab group and 22 (1.1%) women in the alendronate group.
In the placebo-controlled trial of romosozumab for the treatment of osteoporosis in postmenopausal women (including women with severe and less severe osteoporosis) during the 12-month double-blind romosozumab treatment phase, there was no difference in positively adjudicated MACE; 30 (0.8%) occurred in the romosozumab group and 29 (0.8%) in the placebo group. All-cause death occurred in 29 women (0.8%) in the romosozumab group and 24 (0.7%) women in the placebo group.

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 via :
HPRA Pharmacovigilance Website: www.hpra.ie.
By reporting side effects you can help provide more information on the safety of this medicine.

4.9 Overdose

There is no experience with overdose in clinical trials. There is no known antidote to romosozumab or specific treatment for overdose. In case of overdose, it is recommended that patients are monitored closely and given appropriate treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for treatment of bone diseases, drugs affecting bone structure and mineralization, ATC code: M05BX06.

Mechanism of action

Romosozumab is a humanized monoclonal antibody (IgG2) that binds and inhibits sclerostin, thereby increasing bone formation due to the activation of bone lining cells, increasing bone matrix production by osteoblasts, and recruitment of osteoprogenitor cells. Additionally, romosozumab results in changes to expression of osteoclast mediators, thereby decreasing bone resorption. Together, this dual effect of increasing bone formation and decreasing bone resorption results in rapid increases in trabecular and cortical bone mass, improvements in bone structure, and strength.

Pharmacodynamic effects

In postmenopausal women with osteoporosis, romosozumab increased the bone formation marker procollagen Type 1 N terminal propeptide (P1NP) early in treatment, with a peak increase of approximately 145% relative to placebo 2 weeks after initiating treatment, followed by a return to placebo levels at month 9 and a decline to approximately 15% below placebo at month 12. Romosozumab decreased the bone resorption marker type-1 collagen C-telopeptide (CTX) with a maximal reduction of approximately 55% relative to placebo 2 weeks after initiating treatment. CTX levels remained below placebo and were approximately 25% below placebo at month 12.

After discontinuation of romosozumab therapy in postmenopausal women with osteoporosis, P1NP levels returned to baseline within 12 months; CTX increased above baseline levels within 3 months and returned toward baseline levels by month 12, reflecting reversibility of effect. Upon retreatment with romosozumab (in a limited number of patients) after 12 months placebo treatment, the levels of increase in P1NP and decrease in CTX by romosozumab were similar to that observed during the initial treatment.

Clinical trial efficacy

Treatment of osteoporosis in postmenopausal women

Efficacy and safety of romosozumab was assessed in two pivotal studies, an alendronate-controlled (ARCH) and a placebo-controlled study (FRAME).

Study 20110142 (ARCH)

The efficacy and safety of romosozumab in the treatment of osteoporosis in postmenopausal women was evaluated in a multicenter, multinational, randomized, double-blind, alendronate-controlled, superiority study of 4,093 postmenopausal women aged 55 to 90 years (mean age of 74.3 years) with previous fragility fractures.

Enrolled women had either a BMD (Bone Mineral Density) T-score at the total hip or femoral neck of ≤ −2.50, and either at least 1 moderate or severe vertebral fracture; or at least 2 mild vertebral fractures; or a BMD T-score at the total hip or femoral neck of ≤ -2.00, and either at least 2 moderate or severe vertebral fractures; or a fracture of the proximal femur that occurred within 3 to 24 months prior to randomization.

The mean baseline lumbar spine, total hip, and femoral neck BMD T-scores were -2.96, -2.80, and -2.90, respectively, 96.1% of women had a vertebral fracture at baseline, and 99.0% of women had a previous osteoporotic fracture. Women were randomized (1:1) to receive either monthly subcutaneous injections of romosozumab or oral weekly alendronate in a blinded fashion for 12 months. After the 12-month double blind study period, women in both arms transitioned to alendronate while remaining blinded to their initial treatment. The primary analysis was performed when all women had completed the month 24 study visit and clinical fracture events were confirmed for at least 330 women and occurred after a median follow-up time of approximately 33 months on study. Women received calcium and vitamin D supplementation daily.

The primary efficacy endpoints were the incidence of new vertebral fracture through month 24 and the incidence of clinical fracture (nonvertebral fracture and clinical vertebral fracture) at primary analysis.

Effect on new vertebral, clinical, nonvertebral, hip and major osteoporotic fractures
As shown in Table 1, romosozumab reduced the incidence of new vertebral fracture through month 24 (adjusted p-value < 0.001) and the incidence of clinical fracture at primary analysis (adjusted p-value < 0.001) as well as the incidence of non vertebral fractures at primary analysis (adjusted p-value = 0.040) versus treatment with alendronate alone. Table 1 also shows nonvertebral, hip and major osteoporotic fracture risk reduction through primary analysis, month 12 and month 24.

Table 1. The Effect of romosozumab on the Iincidence and risk of new Vvertebral, clinical, nonvertebral, hip and major osteoporotic fractures in post-menopausal women with osteoporosis

	Proportion of women with fracture		Absolute risk reduction (%) (95% CI)	Relative risk reduction (%) (95% CI)
	Alendronate/ Alendronate (%)	Romosozumab/ Alendronate (%)		
New vertebral				
Through month 12	85/1703 (5.0)	55/1696 (3.2)	1.84 (0.51, 3.17)	36 (11, 54)
Through month 24[a]	147/1834 (8.0)	74/1825 (4.1)	4.03 (2.50, 5.57)	50 (34, 62)
Clinical[b]				
Through month 12	110/2047 (5.4)	79/2046 (3.9)	1.8 (0.5, 3.1)	28 (4, 46)
Primary analysis (median follow-up approx. 33 months)	266/2047 (13.0)	198/2046 (9.7)	NA[c]	27 (12, 39)
Nonvertebral				
Through Month 12	95/2047 (4.6)	70/2046 (3.4)	1.4 (0.1, 2.6)	26 (-1, 46)
Primary analysis (median follow-up approx. 33 months)	217/2047 (10.6)	178/2046 (8.7)	NA[c]	19 (1, 34)
Hip				
Through Month 12	22/2047 (1.1)	14/2046 (0.7)	0.3 (-0.3, 0.9)	36 (-26, 67)
Primary analysis (median follow-up approx. 33 months)	66/2047 (3.2)	41/2046 (2.0)	NA[c]	38 (8, 58)
Major osteoporotic[d]				
Through Month 12	85/2047 (4.2)	61/2046 (3.0)	1.4 (0.3, 2.5)	28 (-1, 48)
Primary analysis (median follow-up approx. 33 months)	209/2047 (10.2)	146/2046 (7.1)	NA[c]	32 (16, 45)

a. Absolute risk reduction and relative risk reduction based on Mantel-Haenszel method adjusted for age strata, baseline total hip BMD T-score (≤ -2.5, > -2.5), and presence of severe vertebral fracture at baseline. Treatment comparisons are based on adjusted logistic regression model.

b. Clinical fractures include all symptomatic fractures including nonvertebral and painful vertebral fractures. Treatment comparisons are based on Cox proportional hazards model.

c. NA: not available as subjects have various exposure at primary analysis.

d. Major osteoporotic fractures include hip, forearm, humerus, and clinical vertebral.

Effect on Bone Mineral Density (BMD)

In postmenopausal women with osteoporosis, romosozumab for 12 months followed by alendronate for 12 months increased BMD compared with alendronate alone at month 12 and 24 (p-value < 0.001) (see Table 2).

Following 12 months of treatment, romosozumab increased BMD at the lumbar spine from baseline in 98% of postmenopausal women.

Table 2. Mean percent change in BMD from baseline through month 12 and month 24 in post-menopausal women with osteoporosis

	Alendronate/Alendronate Mean (95% CI) N = 2047[a]	Romosozumab/Alendronate Mean (95% CI) N = 2046[a]	Treatment difference from alendronate-to-alendronate
At Month 12			
Lumbar spine	5.0 (4.8, 5.2)	12.4 (12.1, 12.7)	7.4[b] (7.0, 7.8)
Total hip	2.9 (2.7, 3.1)	5.8 (5.6, 6.1)	2.9[b] (2.7, 3.2)
Femoral neck	2.0 (1.8, 2.2)	4.9 (4.6, 5.1)	2.8[b] (2.5, 3.2)
At Month 24			
Lumbar spine	7.2 (6.9, 7.5)	14.0 (13.6, 14.4)	6.8[b] (6.4, 7.3)
Total hip	3.5 (3.3, 3.7)	6.7 (6.4, 6.9)	3.2[b] (2.9, 3.6)
Femoral neck	2.5 (2.3, 2.8)	5.7 (5.4, 6.0)	3.2[b] (2.8, 3.5)

Means and confidence intervals are based on patients with available data. Based on ANCOVA model; missing values of baseline BMD and BMD percent change from baseline at month 12 and month 24 were imputed by control-based pattern imputation.

a. Number of women randomized
b. p-value < 0.001

The significant difference in BMD achieved in the first 12 months was maintained through month 36 upon transition/continuation to alendronate. Treatment differences were observed at 6 months at lumbar spine, total hip and femoral neck.

Study 20070337 (FRAME)
The efficacy and safety of romosozumab in the treatment of postmenopausal osteoporosis was evaluated in a multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group study of 7,180 postmenopausal women aged 55 to 90 years (mean age of 70.9 years). 40.8% of enrolled women had severe osteoporosis with a prior fracture at baseline.

The co-primary efficacy endpoints were the incidence of new vertebral fractures through month 12 and through month 24.

Romosozumab reduced the incidence of new vertebral fractures through month 12 (absolute risk reduction: 1.3% [95% CI: 0.79; 1.80], relative risk reduction: 73% [95% CI: 53; 84], adjusted p-value < 0.001) and after transition to denosumab through month 24 (absolute risk reduction: 1.89 % [95% CI: 1.30; 2.49], relative risk reduction: 75% [95% CI: 60, 84], adjusted p-value < 0.001).

Women transitioning from bisphosphonate therapy

Study 20080289 (STRUCTURE)

The safety and efficacy of romosozumab in postmenopausal women with severe osteoporosis transitioning from bisphosphonate therapy (92.7% in teriparatide group and 88.1% in romosozumab group had prior alendronate use during the last 3 years) were evaluated in a multicenter, randomized, open-label study of 436 postmenopausal women aged 56 to 90 years (mean age of 71.5 years) versus teriparatide.

The primary efficacy variable was percent change in total hip BMD from baseline at month 12. Romosozumab significantly increased BMD at the total hip relative to teriparatide at month 12 (mean treatment difference from Teriparatide: 3.4% [95% CI: 2.8; 4.0], p-value < 0.0001). The trial was not intended to estimate the effect on fractures but there were seven fractures in the romosozumab arm and nine fractures in the teriparatide arm of the study.

Bone Histology and Histomorphometry

In a bone histology sub-study, a total of 154 transiliac crest bone biopsy specimens were obtained from 139 postmenopausal women with osteoporosis at months 2 and 12 (in FRAME study). Qualitative histology assessments showed normal bone architecture and quality at all time points, normal lamellar bone with no evidence of mineralization defects, woven bone, marrow fibrosis, or clinically significant marrow abnormality in patients treated with romosozumab.

Histomorphometry assessments on biopsies at months 2 and 12 in women showed an increase of bone formation parameters and a decrease in bone resorption parameters while bone volume and trabecular thickness were increased in romosozumab group compared to placebo group.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with romosozumab in one or more subsets of the paediatric population in the treatment of osteoporosis. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption

The median time to maximum romosozumab concentration (t_{max}) was 5 days (range: 2 to 7 days). Following a 210 mg subcutaneous dose, bioavailability was 81%.

Biotransformation

Romosozumab is a humanized monoclonal antibody (IgG2) with high affinity and specificity for sclerostin, and therefore is cleared via a rapid saturable elimination pathway (i.e. target mediated nonlinear clearance, mediated by degradation of the romosozumab-sclerostin complex) and via a slow nonspecific elimination pathway mediated by the reticuloendothelial system.

Elimination

After C_{max}, serum levels declined with a mean effective half-life of 12.8 days. Steady-state was generally reached by month 3 with less than 2-fold accumulation following monthly dosing.

Linearity/non-linearity

Following subcutaneous administration, romosozumab exhibits non-linear pharmacokinetics as a result of binding to sclerostin. Multiple doses administered ranged from 70 to 210 mg.

Renal impairment

Following a 210 mg dose of romosozumab in a clinical trial of 16 patients with severe renal impairment (creatinine clearance < 30 ml/min) or end-stage renal disease (ESRD) receiving haemodialysis, mean Cmax and AUC were 29% and 44% higher in patients with severe renal impairment as compared to healthy subjects. Mean romosozumab exposure was similar in patients with ESRD receiving haemodialysis as compared to healthy subjects.
Population pharmacokinetic analysis indicated an increase in romosozumab exposure with increasing severity of renal impairment. However, based on an exposure-response model of BMD changes and comparison to exposures obtained at tolerated clinical doses, no dose adjustment is recommended in these patients. Monitoring of hypocalcemia in patients with severe renal impairment or receiving dialysis is recommended (see section 4.4).

Hepatic impairment

No clinical trials have been conducted to evaluate the effect of hepatic impairment. Hepatic impairment is not expected to impact on the pharmacokinetics of romosozumab since the liver is not a major organ for romosozumab metabolism or excretion.

Elderly

The pharmacokinetics of romosozumab were not affected by age from 20 years to 89 years.

Bodyweight

Romosozumab exposure decreased with increasing body weight however this decrease had a minimal impact on lumbar spine BMD gain based on exposure-response analysis and is not clinically meaningful. Based on population PK analyses, the expected median steady state AUC for a 61 kg and 114 kg patient is 558 µg.day/ml and 276 µg.day/ml respectively following a monthly subcutaneous dose of 210 mg romosozumab.

Ethnicity and gender

No dose adjustment is necessary for any patient characteristics. Based on a population pharmacokinetic analysis, gender and race (Japanese versus non-Japanese) had no clinically meaningful impact on the pharmacokinetics of romosozumab (< 20% change in exposure at steady state).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, carcinogenic potential or in bone safety studies.

In a carcinogenicity study, doses up to 50 mg/kg/week were administered by subcutaneous injection to Sprague-Dawley male and female rats from 8 weeks of age for up to 98 weeks. These doses resulted in systemic exposures that were up to 19 times higher than the systemic exposure observed in humans following a monthly subcutaneous dose of 210 mg romosozumab (based on AUC comparison). Romosozumab caused a dose-dependent increase in bone mass with macroscopic bone thickening at all doses. There were no effects of romosozumab on mortality or tumor incidence in male or female rats.

Studies in female and male rats did not show any romosozumab-related effects on mating, fertility, or male reproductive assessments (sperm parameters or organ weights), and there were no effects on estrous cycling or any ovarian or uterine parameters at exposures around 54 times the clinical exposure.

Skeletal malformations, including syndactyly and polydactyly, were observed at a low incidence in 1 out of 75 litters at exposures around 30 times the clinical exposure following administration of romosozumab to rats during the period of organogenesis. There were no adverse effects on postnatal growth and development.

Sclerostin has been suggested to have a role in digit formation, however, as digit formation in the human occurs in the first trimester when placental transfer of immunoglobulins is limited, the risk of a similar finding in humans is low (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium acetate
Glacial acetic acid
Sodium hydroxide (for pH adjustment)
Sucrose
Polysorbate 20
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

When taken out of the refrigerator for use, EVENITY should not be returned to the refrigerator but can be kept at room temperature (up to 25°C) for up to 30 days in the original container. If not used within this period, the product should be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.
Keep the pre-filled syringe or pre-filled pen in the outer carton in order to protect from light.

6.5 Nature and contents of container

EVENITY 105 mg solution for injection in pre-filled pen

A single use, disposable, handheld, mechanical injection device pre-assembled with pre-filled syringe containing 1.17 ml solution. The syringe inside the pen is made from cyclo olefin polymer plastic with a stopper (chlorobutyl) and insert molded stainless steel needle with elastomeric needle shield (synthetic rubber).

Pack size of 2 pre-filled pens.
Multipack containing 6 (3 packs of 2) pre-filled pens.

EVENITY 105 mg solution for injection in pre-filled syringe

A single use, disposable, pre-filled syringe containing 1.17 ml solution. The syringe is made from cyclo olefin polymer plastic with a stopper (chlorobutyl) and insert molded stainless steel needle and elastomeric needle shield (synthetic rubber).

Pack size of 2 pre-filled syringes.
Multipack containing 6 (3 packs of 2) pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The solution should be visually inspected for particles and discoloration prior to administration.
EVENITY should not be used if the solution is discolored, cloudy, or contains particles.

Prior to subcutaneous administration, romosozumab should be allowed to sit at room temperature for at least 30 minutes before injecting. This will help make the injection more comfortable. It should not be warmed in any other way.

Do not shake.

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

7. MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.
Allée de la Recherche, 60
B-1070 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1411/001
EU/1/19/1411/002
EU/1/19/1411/003
EU/1/19/1411/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 December 2019
Date of latest renewal: 22 August 2024

10. DATE OF REVISION OF THE TEXT

22 August 2024

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu