NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Stoboclo 60 mg/mL solution for injection pre-filled syringe with automatic needle guard

Stoboclo (denosumab) is a biosimilar medicine to Prolia® (denosumab).

The prescribing physician should be involved in any decision regarding interchangeability (unless the product is known to be non-interchangeable). Additional information is available on the following website (www.medsafe.govt.nz/profs/RIss/Biosimilars.asp). The comparability of Stoboclo with Prolia® has been demonstrated with regard to physicochemical characteristics and efficacy and safety outcomes [see section 5.1 Pharmacodynamic properties, 5.2 Pharmacokinetic Properties and 4.8 Undesirable effects].

The evidence for comparability supports the use of Stoboclo for the listed indications.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL single-use pre-filled syringe contains 60 mg of denosumab in 1 mL (60 mg/mL).

Denosumab is produced in genetically engineered mammalian (Chinese Hamster Ovary, CHO) cells.

Excipient(s) with known effect

Each mL of solution contains 47 mg sorbitol (E420) (see section 4.4).

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Solution for injection.

Stoboclo is supplied as a sterile, preservative-free, clear, colourless to slightly yellow solution for injection at pH 5.2. The solution should not be used if cloudy or discoloured. The solution may contain trace amounts of translucent to white proteinaceous particles.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

The treatment of osteoporosis in postmenopausal women. Stoboclo significantly reduces the risk of vertebral, non-vertebral and hip fractures.

Treatment to increase bone mass in men with osteoporosis at increased risk of fracture.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Dose

The recommended dose of Stoboclo is a single subcutaneous (SC) injection of 60 mg, once every 6 months. If Stoboclo treatment is discontinued, consider transitioning to an alternative antiresorptive therapy.

To reduce the risk of hypocalcaemia, patients must be adequately supplemented with calcium and vitamin D (see section 4.4, Hypocalcaemia). In the major clinical trials of denosumab, daily supplementation with 1000 mg of calcium and at least 400 IU vitamin D was recommended.

Elderly patients
No dose adjustment is necessary in elderly patients (see section 4.4 Use in the Elderly).

Renal impairment
No dose adjustment is necessary in patients with renal impairment (see section 4.4 Use in renal impairment).

Hepatic Impairment
The safety and efficacy of Stoboclo has not been studied in patients with hepatic impairment.

Paediatric population
Stoboclo is not indicated for use in paediatric patients (see section 4.4 Paediatric population).

Method of administration

Stoboclo is a sterile and preservative-free product. Before administration, the Stoboclo solution should be inspected for particulate matter and discolouration. Do not use if the solution is cloudy or discoloured. Do not excessively shake the pre-filled syringe. 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.

Product is for single-use in one patient only. Dispose of any medicinal product remaining in the pre-filled syringe.

4.3 CONTRAINDICATIONS

Hypocalcaemia (See section 4.4).

Hypersensitivity to the active substance, to CHO-derived proteins or to any of the excipients listed in section 6.1.

Pregnancy and in women trying to get pregnant (See section 4.6).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypocalcaemia

Hypocalcaemia must be corrected prior to initiating therapy with denosumab. In the post-marketing setting, severe symptomatic hypocalcaemia (resulting in hospitalisation, life-threatening events and fatal cases) has been reported (see section 4.8), particularly in patients with severe renal impairment, receiving dialysis or treatment with other calcium lowering drugs. While most cases

occurred in the first few weeks of initiating therapy, it has also occurred later. Clinical monitoring of calcium levels is recommended before each dose.

In patients predisposed to hypocalcaemia (e.g. history of hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment [creatinine clearance < 30 mL/min], receiving dialysis or treatment with other calcium lowering drugs), clinical monitoring of calcium levels is recommended during treatment, especially in the first two weeks of initiating therapy.

Hypocalcaemia following denosumab administration is a significant risk in patients with severe renal impairment [creatinine clearance < 30 mL/min], receiving dialysis or treatment with other calcium lowering drugs. Concomitant use of calcimimetic drugs may worsen the risk of hypocalcaemia.

Instruct all patients about the symptoms of hypocalcaemia and the importance of maintaining calcium levels with adequate calcium and vitamin D supplementation.

Adequate intake of calcium and vitamin D is important in all patients (see section 4.2 and section 4.8).

Skin Infections

Patients receiving denosumab may develop skin infections (predominantly cellulitis) leading to hospitalisation (see section 4.8). Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported in patients treated with denosumab or bisphosphonates, another class of antiresorptive agents. Most cases have been in cancer patients; however some have occurred in patients with osteoporosis.

ONJ has been reported rarely in clinical studies in patients receiving denosumab at a dose of 60 mg every 6 months for osteoporosis. There have been reports of ONJ in clinical studies in patients with advanced cancer treated with denosumab at the studied dose of 120 mg administered monthly.

Known risk factors for ONJ include a diagnosis of cancer with bone lesions, concomitant therapies (e.g. chemotherapy, antiangiogenic biologics, corticosteroids, radiotherapy to head and neck), poor oral hygiene, invasive dental procedures (e.g. tooth extraction), and co-morbid disorders (e.g. pre-existing dental disease, anaemia, coagulopathy, infection). The risk of ONJ may increase with duration of exposure to denosumab.

It is important to evaluate patients for risk factors for ONJ before starting treatment. If risk factors are identified, a dental examination with appropriate preventive dentistry is recommended prior to treatment with denosumab. Good oral hygiene practices should be maintained during treatment with denosumab.

Avoid invasive dental procedures during treatment with denosumab. For patients in whom invasive dental procedures cannot be avoided, the clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Patients who are suspected of having or who develop ONJ while on denosumab should receive care by a dentist or an oral surgeon. In patients who develop ONJ during treatment with denosumab, a temporary interruption of treatment should be considered based on individual risk/benefit assessment until the condition resolves.

Atypical Femoral Fractures

Atypical femoral fractures have been reported in patients receiving denosumab. Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur and may be bilateral. 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 pharmaceutical agents (e.g. bisphosphonates, glucocorticoids, proton pump inhibitors). These events have also occurred without antiresorptive therapy. During denosumab 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, and the contralateral femur should also be examined.

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.

Patients being treated with denosumab, should be advised not to interrupt denosumab therapy without prior consultation with their treating physician. The individual benefit/risk should be evaluated before discontinuing treatment with denosumab. If denosumab treatment is discontinued, consider transitioning to an alternative antiresorptive therapy.

Hypercalcaemia in Paediatric Patients with Osteogenesis Imperfecta

Denosumab is not indicated for use in paediatric patients. In clinical trials, hypercalcaemia has been reported in paediatric patients with osteogenesis imperfecta treated with denosumab. Some cases required hospitalisation (see section 4.4 Paediatric population).

Medicines with Same Active Ingredient

Stoboclo contains the same active ingredient found in Xgeva® (denosumab) and Osenvelt (denosumab), used for the treatment of skeletal related events in patients with bone metastasis from solid tumours. Patients being treated with Stoboclo should not be treated with Xgeva® or Osenvelt concomitantly.

Excipients with Known Effects

Stoboclo contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not use Stoboclo.

Stoboclo contains less than 1 mmol sodium (23 mg) per 60 mg, i.e. essentially ‘sodium free’.

Paediatric population

Stoboclo is not indicated for use in paediatric patients. In clinical trials, hypercalcaemia has been reported very commonly in paediatric patients with osteogenesis imperfecta treated with denosumab. Some cases required hospitalisation and were complicated by acute renal injury (see section 4.4 Hypercalcaemia in Paediatric Patients with Osteogenesis Imperfecta). Adolescent

primates dosed with denosumab at 27 and 150 times (10 and 50 mg/kg dose) the clinical exposure based on AUC had abnormal growth plates. In neonatal rats, inhibition of RANKL (target of denosumab therapy) with a construct of osteoprotegerin bound to immunoglobulin Fc segment (OPG-Fc) at high doses was associated with inhibition of bone growth and tooth eruption. Therefore, treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition.

Use in renal impairment

No dose adjustment is necessary in patients with 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. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis (see Hypocalcaemia).

Use in the Elderly

Of the total number of patients in clinical studies of denosumab, 9,943 patients were ≥ 65 years, while 3,576 were ≥ 75 years. No overall differences in safety or efficacy were observed between these patients and younger patients.

Of the patients in the osteoporosis study in men, 133 patients (55%) were ≥ 65 years old, while 39 patients (16%) were ≥ 75 years old.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Calcimimetics: Concomitant use of calcimimetic drugs (e.g. cinacalcet) may worsen the risk of hypocalcaemia.

In an interaction study conducted on 17 postmenopausal women with osteoporosis, midazolam (2 mg oral) was administered two weeks after a single dose of denosumab (60 mg subcutaneous injection), which approximates the T_{max} of denosumab. 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 medicines metabolised by CYP3A4.

No interactions with laboratory and diagnostic tests have been identified.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Pregnancy Category D

There are no adequate and well-controlled studies of denosumab in pregnant women. Denosumab is contraindicated for use during pregnancy and in women trying to get pregnant.

Developmental toxicity studies have been performed with denosumab in cynomolgus monkeys and have shown serious adverse events on the development (including fetal and infant lethality). Denosumab was shown to cross the placenta in monkeys.

In a study of cynomolgus monkeys with denosumab at subcutaneous doses up to 12.5 mg/kg/week, given during the period equivalent to the first trimester, and yielding AUC exposures up to 99-fold higher than the human exposure (60 mg every 6 months), there was no evidence of maternal or fetal harm. In this study fetal lymph nodes were not examined.

In another study of cynomolgus monkeys dosed with denosumab throughout pregnancy at 50 mg/kg/month, yielding AUC exposures 119-fold higher than the human exposure, there were increased stillbirths and postnatal mortality; abnormal bone growth resulting in reduced bone strength, almost complete obliteration of bone marrow spaces (leading to reduced haematopoiesis), and tooth malalignment, dental dysplasia and a shortened/straighter dental arch (although no effect on the pattern or date of tooth eruption); altered appearance of eyes (increased apparent size, exophthalmos); absence of peripheral lymph nodes; and decreased neonatal growth. Following a 6 month period after birth, bone-related changes showed incomplete recovery. The effects on lymph nodes, tooth malalignment and dental dysplasia persisted, and minimal to moderate mineralisation in multiple tissues was seen in one animal. There was no evidence of maternal harm prior to labour; adverse maternal effects occurred infrequently during labour. Maternal mammary gland development was normal. A no observed adverse effect level has not been established in animal studies and the findings are attributable to the primary pharmacological activity of denosumab.

Knockout mice lacking RANK or RANKL (1) had an absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development during pregnancy) (2) exhibited impairment of lymph node formation (3) exhibited reduced bone growth and lack of tooth eruption. Similar phenotypic changes were seen in a corroborative study in 2-week old rats given the RANKL inhibitor OPG-Fc. Therefore, treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition. These changes were partly reversible in this model when dosing with the RANKL inhibitors was discontinued.

Studies in RANK/RANKL knockout mice suggest absence of RANKL during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum.

Breast-feeding

It is unknown whether denosumab is excreted in human milk. Only limited excretion of denosumab in milk was observed in a study in monkeys. A decision on whether to abstain from breast-feeding or to abstain from therapy with denosumab should be made, taking into account the benefit of breast-feeding to the newborn/infant and the benefit of denosumab therapy to the woman.

Fertility

No data are available on the effect of denosumab on human fertility. Denosumab had no effect on female fertility or male reproductive organs or sperm motility in cynomolgus monkeys at subcutaneous doses up to 12.5 mg/kg/week (females) or 50 mg/kg/month (males), yielding exposures that were approximately 150-fold higher than the human exposure at 60 mg subcutaneous administered once every 6 months.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive or use machinery have been performed.

4.8 UNDESIRABLE EFFECTS

Summary of safety profile

Treatment of Postmenopausal Osteoporosis
Denosumab has been studied in over 10,500 women with postmenopausal osteoporosis in clinical trials representing up to 8 years of continued denosumab treatment.

The safety of denosumab in the treatment of postmenopausal osteoporosis was assessed in FREEDOM, a large, 3-year, randomised, double-blind, placebo-controlled, multinational phase III study of 7,808 postmenopausal women aged 60 to 91 years with osteoporosis. A total of 3,886 women were exposed to denosumab and 3,876 women were exposed to placebo administered once every 6 months as a single 60 mg subcutaneous dose.

The safety of denosumab was also assessed in a second phase 3 study of similar design. A total of 322 postmenopausal women aged 43 to 83 years with low bone mass were enrolled in this 2-year study. A total of 164 women were exposed to denosumab and 165 women were exposed to placebo administered once every 6 months as a single 60 mg subcutaneous dose.

In both studies, all women received at least 1000 mg of calcium and 400 IU of vitamin D supplementation per day.

Across the two phase III studies the incidence of all-cause mortality was 1.7% (n = 70) in the denosumab group and 2.2% (n = 90) in the placebo group. The incidence of serious adverse events was 25.3% in the denosumab group and 24.3% in the placebo group. The percentage of patients who withdrew from the studies due to adverse events was 2.3% and 2.1% for the denosumab and placebo groups, respectively.

The most common adverse events reported in studies of women with postmenopausal osteoporosis or low bone mass (n = 8,091), occurring in ≥ 10% of patients either in the denosumab-treated or placebo group, were back pain (34.1% denosumab, 34.0% placebo), arthralgia (20.4% in each group), hypertension (15.3% denosumab, 16.1% placebo), nasopharyngitis (14.8% denosumab, 15.6% placebo), pain in extremity (11.8% denosumab, 11.2% placebo) and osteoarthritis (10.9% denosumab, 11.1% placebo).

Adverse events reported in at least 2% of postmenopausal women with osteoporosis or low bone mass (n = 8,091) and at least 1% more frequently in the denosumab-treated women than in the placebo-treated women were: hypercholesterolemia (7.0% denosumab, 5.9% placebo) and eczema (includes dermatitis, allergic dermatitis, atopic dermatitis and contact dermatitis) (3.1% denosumab, 1.7% placebo).

In STAND, a double-blind, randomised, alendronate-controlled, study in postmenopausal women with low bone mass who had received alendronate for at least 6 months preceding study entry, patients received either denosumab 60 mg Q6M SC (n = 253) or alendronate orally 70 mg weekly for 12 months (n = 249). The safety profile was similar for patients transitioning from alendronate to denosumab and those continuing on alendronate therapy, including the overall incidence of adverse events and serious adverse events. Eight patients (3.2%) in the denosumab group and 4 patients (1.6%) in the alendronate group reported adverse events of fracture.

Tabulated list of adverse reactions

The data in Table 1 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.

Table 1 Adverse Reactions

System Organ Class	Very common ≥ 10%	Common ≥ 1% and < 10%	Uncommon ≥ 0.1% and < 1%	Rare ≥ 0.01% and < 0.1%
Immune system disorders				Hypersensitivity reactions [a]
Infections and infestations			Skin infections [b] leading to hospitalization	
Metabolism and nutrition disorders				Hypocalcaemia Severe symptomatic hypocalcaemia[c]
Skin and subcutaneous tissue disorders		Eczema [d]		
Musculoskeletal and connective tissue disorders	Pain in extremity Musculoskeletal pain[e]		Multiple vertebral fractures following discontinuation of denosumab[f]	Osteonecrosis of the jaw Atypical femoral fracture

[a] including rash, urticarial, facial swelling, erythema and anaphylactic reactions

[b] predominantly cellulitis

[c] reported in patients at increased risk of hypocalcaemia receiving denosumab

[d] includes dermatitis, allergic dermatitis, atopic dermatitis, and contact dermatitis

[e] including severe cases

[f] particularly in those with a history of vertebral fracture

Description of selected adverse reactions

Hypocalcaemia

In two phase III placebo-controlled clinical trials in postmenopausal women with osteoporosis, approximately 0.05% (2 of 4,050) of patients had declines of serum calcium levels (less than 1.88 mmol/L) following denosumab administration.

Skin Infections

In two phase III placebo-controlled clinical trials in postmenopausal women with osteoporosis, skin infections leading to hospitalisation were reported more frequently in the denosumab (0.4%, 16 of 4,050) versus the placebo (0.1%, 3 of 4,041) groups, respectively. These cases were predominantly cellulitis. The overall incidence of skin infections was similar between the denosumab (1.5%, 59 of 4,050) and placebo groups (1.2%, 50 of 4,041).

Pancreatitis
Pancreatitis was reported in 4 patients (0.1%) in the placebo and 8 patients (0.2%) in the denosumab groups. Several patients had a prior history of pancreatitis or a confounding event (e.g. gallstones). The time from product administration to event occurrence was variable.

Osteonecrosis of the Jaw (ONJ)
In the osteoporosis clinical trial program, ONJ was reported rarely in patients treated with denosumab.

Atypical Femoral Fractures
In the osteoporosis clinical trial program, atypical femoral fractures were reported rarely in patients treated with denosumab.

Multiple Vertebral Fractures (MVF) Following Discontinuation of denosumab Treatment
In the osteoporosis clinical trial program, MVF were reported in patients following discontinuation of treatment with denosumab, particularly in those with a history of vertebral fracture.

Long Term Safety in Postmenopausal Osteoporosis

A total of 4550 women who completed FREEDOM (Study 20030216, N = 7808) enrolled into FREEDOM Extension (Study 20060289), a 7-year, multinational, multicenter, open-label, single-arm extension study to evaluate the long-term safety and efficacy of denosumab. All patients in the extension study receive denosumab every 6 months as a single SC 60 mg dose, as well as daily calcium (1000 mg) and vitamin D (at least 400 IU).

During the FREEDOM Extension study, the rates of adverse events observed through month 60 have not shown an increase over time and were similar to those observed in the initial 3 years of FREEDOM. Eight adjudicated cases of osteonecrosis of the jaw (ONJ) and two atypical fractures of the femur have occurred during the extension study.

Treatment of Osteoporosis in Men

The safety of denosumab in the treatment of men with osteoporosis was assessed in ADAMO, a randomised, double-blind, placebo-controlled study; a 1 year double-blind phase followed by a 1 year open-label extension. During the double-blind phase, a total of 120 men were exposed to denosumab and 120 men were exposed to placebo administered subcutaneously once every 6 months as a single 60 mg dose. All men were instructed to take at least 1000 mg of calcium and 800 IU of vitamin D supplementation per day.

The incidence of all-cause mortality was 0.8% (n = 1) in the denosumab group and 0.8% (n = 1) in the placebo group. The incidence of serious adverse events was 9.2% in the denosumab group and 8.3% in the placebo group. The percentage of patients who withdrew from the study due to adverse events was 2.5% and 0% for the denosumab and placebo groups, respectively.

Adverse events in men with osteoporosis (n=240) occurring in at least 5% of denosumab -treated men and more frequently than in the placebo-treated patients were: back pain (8.3% denosumab, 6.7% placebo), arthralgia (6.7% denosumab, 5.8% placebo), and nasopharyngitis (6.7% denosumab, 5.8% placebo).

Post marketing Experience
Rare events of medicine-related hypersensitivity reactions: rash, urticaria, facial swelling, erythema and anaphylactic reactions.

Rare events of severe symptomatic hypocalcaemia (resulting in hospitalisation, life-threatening events, and fatal cases) have been reported predominantly in patients at increased risk of hypocalcaemia, particularly in patients with severe renal impairment, receiving dialysis or treatment with other calcium lowering drugs receiving denosumab. Most cases occurred in the first weeks of initiating therapy. Examples of the clinical manifestations of severe symptomatic hypocalcaemia have included QT prolongation, tetany, seizures and altered mental status (see section 4.4 Hypocalcaemia). Symptoms of hypocalcaemia in denosumab clinical studies included paraesthesia, muscle stiffness, twitching, spasms and muscle cramps.

Musculoskeletal pain, including severe cases, has been reported in patients receiving denosumab.

Very rare events of hypersensitivity vasculitis.

Uncommon events of lichenoid drug eruptions (e.g. lichen planus-like reactions) have been observed.

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome has been observed.

Common events of alopecia have been reported.

Comparability of Stoboclo with Prolia®

Adverse Events
There were no notable differences in the incidence or nature of Adverse Events (AEs) between the CT-P41 (Stoboclo) and Prolia® treatment groups across Studies CT-P41 3.1, CT-P41 1.2, and CT-P41 1.1, and safety profile of each treatment group was in line with the known safety profile of Prolia®. As a result, the analysis of AEs obtained in the clinical studied with CTP41 illustrated that the benefit-risk profile of CT-P41 is similar to that of Prolia®.

Immunogenicity
The immunogenicity of CT-P41 was evaluated in healthy male subjects in Studies CT-P41 1.2 and CT-P41 3.1 in postmenopausal women with osteoporosis using the state-of-the-art and validated immunogenicity assays in accordance with the current international regulatory guidelines.

In both healthy male subjects and postmenopausal women with osteoporosis, the anti-drug antibody (ADA) responses were comparable between the treatment groups in terms of incidence and titer. The incidence of ADA was higher compared to that of historical studies conducted with Prolia®. Only 2 subjects in each treatment group of Study CT-P41 1.2 tested NAb positive and no patient had a NAb positive result in Study CT-P41 3.1. Further post-hoc analyses showed there was no discernible impact of ADA on Pharmacokinetics (PK), Pharmacodynamics (PD), efficacy and safety in Studies CT-P41 1.2 and CT-P41 3.1.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 OVERDOSE

There is no experience with overdosage with denosumab. Denosumab has been administered in clinical studies using doses up to 180 mg every 4 weeks (cumulative doses up to 1080 mg over 6 months), and no additional adverse effects were observed.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

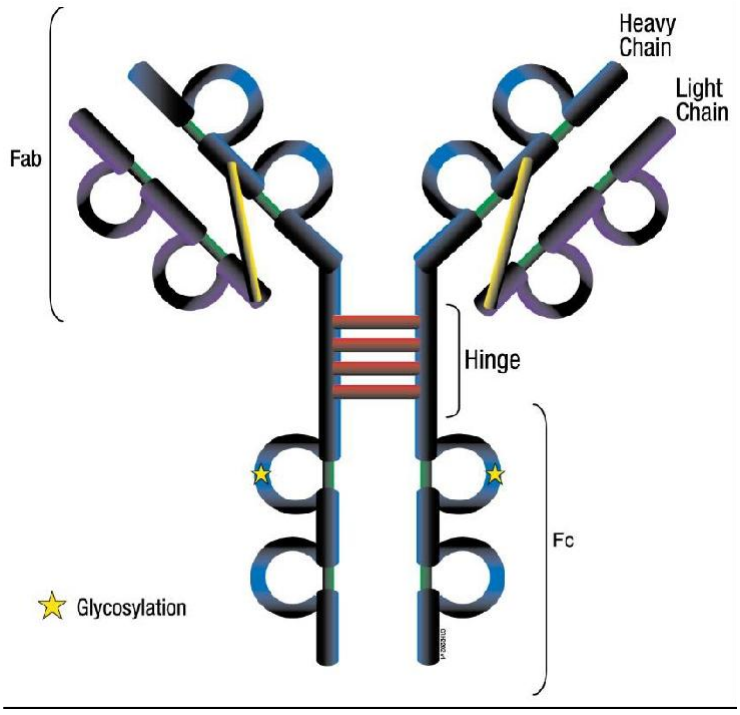
5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Denosumab is a fully human IgG2 monoclonal antibody with high affinity and specificity for RANK ligand (RANKL). Denosumab has an approximate molecular weight of 147 kDa.

CAS number: 615258-40-7



Pharmacodynamic effects

Mechanism of Action
RANKL exists as a transmembrane or soluble protein. RANKL is essential for the formation, function and survival of osteoclasts, the sole cell type responsible for bone resorption. Osteoclasts play an important role in bone loss associated with postmenopausal osteoporosis and hormone ablation. Denosumab binds with high affinity and specificity to RANKL, preventing RANKL from activating its only receptor, RANK, on the surface of osteoclasts and their precursors, independent of bone surface. Prevention of RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone.

Pharmacodynamics
In clinical studies, treatment with 60 mg of denosumab resulted in rapid reduction in the bone resorption marker serum type 1 C-telopeptides (CTX) within 6 hours of SC administration by approximately 70%, with reductions of approximately 85% occurring by 3 days. CTX reductions were maintained over the 6-month dosing interval. At the end of each dosing interval, CTX reductions were partially attenuated from maximal reduction of ≥ 87% to ≥ 45% (range 45% to 80%), reflecting the reversibility of the effects of denosumab on bone remodelling once serum denosumab levels diminish. These effects were sustained with continued treatment. Consistent with the physiological coupling of bone formation and resorption in skeletal remodeling, subsequent reductions in bone formation markers (e.g. bone specific alkaline phosphatase [BSAP] and serum N-terminal propeptide of type 1 collagen [P1NP]) were observed beginning 1 month after the first dose of denosumab.

Bone turnover markers (bone resorption and formation markers) generally reached pretreatment levels within 9 months after the last 60 mg subcutaneous dose. Upon re-initiation, the degree of inhibition of CTX by denosumab was similar to those observed in patients initiating denosumab.

In a clinical study of postmenopausal women with low bone mass (n = 504) who were previously treated with alendronate for a median of 3 years, those transitioning to receive denosumab experienced additional reductions in serum CTX, compared with women who remained on alendronate. In this study, the changes in serum calcium were similar between the two groups.

Comparability of Stoboclo with Prolia®
The pharmacodynamic comparability of Stoboclo was demonstrated in a Phase I study in 154 healthy subjects comparing Stoboclo with Prolia® (CT-P41 1.2). The study evaluated PK/PD after a single dose of Stoboclo or Prolia® 60 mg/1 mL as a subcutaneous injection to the upper arm via a pre-filled syringe. The pharmacodynamic comparability of Stoboclo with Prolia® was further demonstrated in the Phase II study in 479 postmenopausal women (CT-P41 3.1). Endpoints in both studies included the area under the effect curve (AUEC) of CTX and P1NP which were based on the percent change from baseline (% inhibition). Overall across both studies, the geometric LS mean (SD) values of AUECs of CTX and P1NP were similar between the 2 treatment groups. Furthermore, the ratio of geometric LS means of AUEC for CTX and P1NP with the associated 95% CIs indicated similarity between the 2 treatment groups in each of the studies.

Clinical efficacy and safety

Treatment of osteoporosis in postmenopausal women
Independent risk factors, for example, low bone mineral density (BMD), age, the existence of previous fracture, family history of hip fractures, high bone turnover and low body mass index (BMI) should be considered in order to identify women at increased risk of osteoporotic fractures who could benefit from treatment.

Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM): The efficacy and safety of denosumab in the treatment of postmenopausal osteoporosis was demonstrated in FREEDOM (Study 20030216), a 3-year, randomised, double-blind, placebo-controlled, multinational study of women with baseline BMD T-scores at the lumbar spine or total hip between -2.5 and -4.0. 7,808 women aged 60 to 91 years were enrolled of whom 23.6% had prevalent vertebral fractures. Women with other diseases or on therapies that may affect bone (e.g. rheumatoid arthritis, osteogenesis imperfecta and Paget's disease) were excluded from this study.

BMD and other individual risk factors were collected for women enrolled in the FREEDOM study. The mean absolute 10-year fracture probability for women enrolled was 18.60% (deciles: 7.9-32.4%) for major osteoporotic fracture and 7.22% (deciles: 1.4 - 14.9%) for hip fracture, as derived from FRAX®, the WHO Fracture Risk Assessment Tool algorithm.

Women were randomised to receive subcutaneous injections of either denosumab 60 mg (n = 3,902) or placebo (n = 3,906) once every 6 months. Women received calcium (at least 1,000 mg) and vitamin D (at least 400 IU) supplementation daily. The primary efficacy variable was the incidence of new vertebral fractures. Secondary efficacy variables included the incidence of non-vertebral fractures and hip fractures, assessed at 3 years.

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

Table 2 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)
	Denosumab n = 3,902 (%)	Placebo n = 3,906 (%)		
0-1 Year	0.9	2.2	1.4 (0.8, 1.9)	61 (42, 74)*
0-2 Years	1.4	5.0	3.5 (2.7, 4.3)	71 (61, 79)*
0-3 Years	2.3	7.2	4.8 (3.9, 5.8)	68 (59, 74)*

*$p < 0.0001$

The reductions in the risk of new vertebral fractures by denosumab over 3 years were consistent and significant regardless of whether or not women had a prevalent vertebral fracture or history of a non-vertebral fracture, and regardless of baseline age, BMD, bone turnover level and prior use of a medicinal product for osteoporosis.

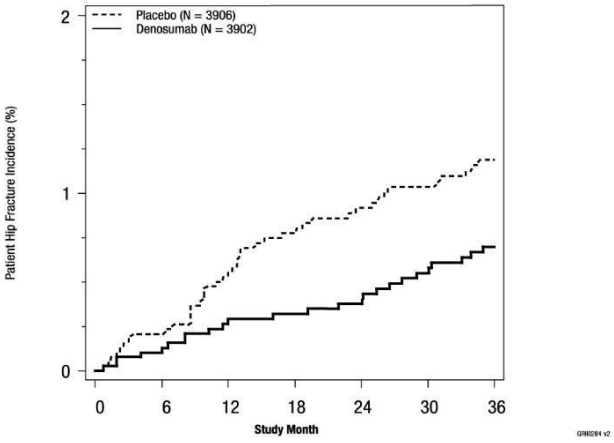
Denosumab also reduced the risk of new vertebral fracture by 65% (6.5% absolute risk reduction, $p < 0.0001$) in patients at high risk of fractures (defined as women who met ≥ 2 of the 3 following criteria at baseline: age ≥ 70 years, BMD T-score ≤ -3.0 [at lumbar spine, total hip, or femoral neck] or prevalent vertebral fracture).

Denosumab also reduced the risk of new and worsening vertebral fractures (67% relative risk reduction, 4.8% absolute risk reduction) as well as multiple vertebral fractures (61% relative risk reduction, 1.0% absolute risk reduction) at 3 years, when compared to placebo (all $p < 0.0001$).

Effect on hip fractures

Denosumab demonstrated a 40% relative reduction (0.5% absolute risk reduction) in the risk of hip fracture over 3 years ($p < 0.05$) (see Figure 1). The incidence of hip fracture was 0.7% in the denosumab group compared to 1.2% in the placebo group at 3 years.

Figure 1 Cumulative incidence of hip fractures over 3 years



In women with high fracture risk as defined above by baseline age, BMD and prevalent vertebral fracture, a 48% relative risk reduction was observed with denosumab (1.1% absolute risk reduction, $p < 0.05$).

Effect on all clinical fractures

Denosumab demonstrated superiority to placebo in reducing the risk of any clinical fractures, clinical (symptomatic) vertebral fractures, non-vertebral fractures (including hip), major non-vertebral fractures and major osteoporotic fractures (see Table 3).

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

	Proportion of women with fracture (%)		Absolute risk reduction (%)	Relative risk reduction (%)
	denosumab n = 3,902 (%)	Placebo n = 3,906 (%)	(95% CI)	(95% CI)
Any clinical fracture[1]	7.2	10.2	2.9 (1.6, 4.2)	30 (19, 41)***

	Proportion of women with fracture (%)		Absolute risk reduction (%)	Relative risk reduction (%)
	denosumab n = 3,902 (%)	Placebo n = 3,906 (%)	(95% CI)	(95% CI)
Clinical vertebral fracture	0.8	2.6	1.8 (1.2, 2.4)	69 (53, 80)***
Non-vertebral fracture[2]	6.5	8.0	1.5 (0.3, 2.7)	20 (5, 33)**
Major non- vertebral fracture[3]	5.2	6.4	1.2 (0.1, 2.2)	20 (3, 34)*
Major osteoporotic fracture[4]	5.3	8.0	2.7 (1.6, 3.9)	35 (22, 45)***

*p ≤ 0.05; **p = 0.0106, ***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 (cervical, thoracic, and lumbar), skull, facial, mandible, metacarpus, and finger and toe phalanges

(3) Includes pelvis, distal femur (i.e. femur excluding hip), proximal tibia (i.e. tibia excluding ankle), ribs, proximal humerus (i.e. humerus excluding elbow), forearm, and hip

(4) Includes clinical vertebral, hip, forearm, and humerus fractures, as defined by the WHO

Women in the FREEDOM study had a mean baseline BMD T-score of -2.2 at the femoral neck. In women with baseline femoral neck BMD ≤ -2.5, denosumab reduced the incidence of non-vertebral fracture (35% relative risk reduction, 4.1% absolute risk reduction, $p < 0.001$).

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 as assessed by FRAX.

Effect on bone mineral density

Denosumab significantly increased BMD at all clinical sites measured, relative to treatment with placebo at 1, 2 and 3 years in FREEDOM. 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 $p < 0.0001$). Increases in BMD at lumbar spine, total hip and hip trochanter were observed as early as 1 month after the initial dose. Denosumab increased lumbar spine BMD from baseline in 95% of postmenopausal women at 3 years. Consistent effects on BMD were observed at the lumbar spine regardless of baseline age, race, weight/BMI, BMD and bone turnover level. The effects of denosumab on bone architecture were evaluated using quantitative computed tomography (QCT) in postmenopausal women with BMD T-score below -2.5 at the lumbar spine or total hip. Treatment with denosumab increased volumetric trabecular BMD at the lumbar spine, volumetric BMD at the total hip and the volumetric cortical BMD and cortical thickness at the distal radius.

Study of Transitioning from Alendronate to Denosumab (STAND, Study 20050234) was a double-blind, randomised, alendronate-controlled, study in postmenopausal women with low BMD (T score between -2.0 and -4.0 at the lumbar spine or total hip) who had received alendronate (70 mg weekly [or equivalent] orally) for at least 6 months preceding study entry. Patients received either denosumab 60 mg Q6M SC (n = 253) or alendronate orally 70 mg weekly for 12 months (n = 251).

Women who transitioned to receive denosumab had greater increases in BMD at the total hip (1.9% versus 1.1%, $p < 0.001$; primary efficacy endpoint) after 1 year, compared to those who continued to receive alendronate therapy. Consistently greater increases in BMD were also seen at the lumbar spine, femoral neck, hip trochanter, and distal 1/3 radius in women treated with denosumab, compared to those who continued to receive alendronate therapy (all $p < 0.05$).

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 medicine. 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 (FREEDOM Extension Study)

A total of 4550 women, (2343 denosumab and 2207 placebo) who missed no more than one dose of denosumab in the FREEDOM pivotal study (Study 20030216, N = 7808) and completed the month 36 study visit, enrolled in FREEDOM Extension (Study 20060289), a 7-year, multinational, multicenter, open-label, single-arm extension study to evaluate the long-term safety and efficacy of denosumab. All women in the FREEDOM Extension study were to receive denosumab every 6 months in an open-label manner as a single 60 mg SC dose, as well as daily calcium (at least 1000 mg) and vitamin D (at least 400 IU).

Safety was the primary endpoint; BMD and fracture incidence were two of the many secondary endpoints. At month 84 of the extension study, after 10 years of denosumab treatment, the long-term group increased BMD by 21.7% (95% CI: 21.2, 22.2) at the lumbar spine, 9.2% (8.9, 9.5) at the total hip, 9.0% (8.6, 9.4) at the femoral neck and 13.0% (12.6, 13.4) at the trochanter from the pivotal FREEDOM study baseline. In years 4 through 10 of denosumab treatment, the rates of new vertebral and non-vertebral fractures did not increase over time; annualised rates were approximately 1.0% and 1.3% respectively.

Bone Histology

Fifty-three trans-iliac crest bone biopsy specimens were obtained at either 2 years and/or 3 years from 47 postmenopausal women with osteoporosis treated with denosumab in the FREEDOM study. Fifteen bone biopsy specimens were also obtained after 1 year of treatment with denosumab from 15 postmenopausal women with low bone mass who had transitioned from previous alendronate therapy. Histology assessments in both studies showed bone of normal architecture and quality, as well as the expected decrease in bone turnover relative to placebo treatment. There was no evidence of mineralisation defects, woven bone or marrow fibrosis.

Fifty-nine women participated in the bone biopsy sub-study at month 24 (N = 41) and/or month 84 (N = 22) of the FREEDOM extension study, representing up to 5 and 10 years of treatment with

denosumab, respectively. Bone biopsy results showed bone of normal architecture and quality with no evidence of mineralisation defects, woven bone or marrow fibrosis as well as the expected decrease in bone turnover.

Histomorphometry findings in the FREEDOM 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.

Treatment of Osteoporosis in Men

A Multicenter Randomised Double-blind Placebo Controlled Study to Compare the Efficacy and Safety of Denosumab versus Placebo in Males with Osteoporosis (ADAMO):

The efficacy and safety of denosumab in the treatment of men with osteoporosis was demonstrated in ADAMO (Study 20080098), a 1-year, multinational study of men with low bone mass, who had a baseline BMD T-score between -2.0 and -3.5 at the lumbar spine or femoral neck. Men with a BMD T-score between -1.0 and -3.5 at the lumbar spine or femoral neck and with history of prior fragility fracture were also enrolled. Men with other diseases (such as rheumatoid arthritis, osteogenesis imperfecta, and Paget's disease), or with significantly impaired renal function (GFR of ≤ 30 mL/min), or on therapies that may affect bone were excluded from this study.

Table 4 Baseline BMD T-scores (Randomised Subjects)

	Denosumab (N = 121)	Placebo (N = 121)	All (N = 242)
Minimum BMD T-score at lumbar spine or femoral neck	n (%)	n (%)	n (%)
≤ -2.5	61 (50)	56 (46)	117 (48)
> -2.5	60 (50)	65 (54)	125 (52)

N = number of subjects randomised

The 242 men enrolled in the ADAMO study ranged in age from 31 to 84 years and were randomised to receive subcutaneous injections of either denosumab 60 mg (n = 121) or placebo (n = 121) once every 6 months. Men received calcium (at least 1000 mg) and vitamin D (at least 800 IU) supplementation daily.

The primary efficacy variable was percent change in lumbar spine BMD at 1 year. Secondary efficacy variables included percent change in total hip, hip trochanter, femoral neck, and distal 1/3 radius BMD at 1 year, and change in CTX at day 15.

Denosumab significantly increased BMD at all clinical sites measured, relative to treatment with placebo at 1 year in men with osteoporosis. Denosumab increased BMD by 4.8% at the lumbar spine, 2.0% at the total hip, 2.3% at the hip trochanter, 2.2% at the femoral neck and 0.9% at the distal 1/3 radius, relative to placebo. Consistent effects on BMD were observed at the lumbar spine regardless of baseline age, race, weight/body mass index (BMI), BMD, and level of bone turnover.

Bone Histology

A total of 29 trans-iliac crest bone biopsy specimens were obtained from men with osteoporosis at 12 months (17 specimens in denosumab group, 12 specimens in placebo group). Qualitative histology assessments showed normal architecture and quality with no evidence of mineralisation defects, woven bone, or marrow fibrosis.

Comparability of Stoboclo with Prolia®

The clinical comparability between Stoboclo and Prolia® was demonstrated in a double-blind, randomized, active-controlled, phase 3 study in 479 postmenopausal women with osteoporosis.

The study population consisted of postmenopausal female patients with osteoporosis aged 50 to 80 years of age. Postmenopausal was defined by no menstrual period for at least 12 months with follicle-stimulating hormone (FSH) level ≥30 mIU/mL or surgical menopause ≥12 months prior to the Screening visit. Patients were required to have BMD T-score ≤-2.5 and ≥-4.0 at the lumbar spine (L1 to L4) as assessed by the central imaging vendor based on dual-energy X-ray absorptiometry (DXA) scan at Screening.

On Day 1 (Week 0), 479 patients were randomly assigned in a 1:1 ratio to one of the 2 treatment groups to receive 60 mg of Stoboclo or Prolia®. Randomization was balanced by using permuted blocks and was stratified by age (< 65 versus ≥ 65), baseline BMD T-score at the lumbar spine (≤ − 3.0 versus > − 3.0), and prior bisphosphonates therapy (Yes versus No).

The results of the primary efficacy endpoint, mean change from baseline in BMD for lumbar spine (L1 to L4) by DXA at Week 52 between the treatment groups is presented in Table 5 below. In the full analysis set (FAS), the LS mean (SE) of percent change from baseline in BMD for lumbar spine at Week 52 were similar between the Stoboclo and Prolia® treatment groups (4.9317 [0.31508] and 5.0706 [0.32714], respectively). The 95% CI for treatment difference (-0.826, 0.548) was entirely contained within the pre-defined margin of (-1.503, 1.503) indicating therapeutic equivalence between Stoboclo and Prolia®. Similar results were observed in the per-protocol set (PPS) as well (95% CI:-0.973, 0.414), supporting the primary efficacy analysis result with the FAS. Overall, the results from the FAS and PPS consistently demonstrate similarity between Stoboclo and Prolia®.

Table 5 Statistical Analysis of Mean Change from Baseline in BMD for Lumbar Spine at Week 52

	FAS (Multiple Imputation)		PPS (Complete Case Analysis)	
	Stoboclo	Prolia®	Stoboclo	Prolia®
n	222	212	215	202
LS Mean (SE)	4.9317 (0.31508)	5.0706 (0.32714)	5.0330 (0.31640)	5.3125 (0.33505)
Estimate of Treatment difference (90% CI)	-0.139 (-0.826, 0.548)		-0.280 (-0.973, 0.414)	

Abbreviations: ANCOVA, Analysis of covariate; FAS, Full analysis set; n: The number of patients who have a BMD assessment result for Lumbar Spine by DXA at Week 52 in FAS or PPS; PPS, Per-protocol set; LS, Least Squares; SE, Standard Error

Secondary efficacy endpoints included percent change from baseline in BMD for lumbar spine, total hip and femoral neck by DXA at Weeks 26, 52 and 78; incidences of new vertebral, nonvertebral and

hip fractures; change from baseline in health-related quality of life (osteoporosis assessment questionnaire-short version [OPAQ-SV] and EuroQoL-5 dimensions-5 levels health survey [EQ-5D-5L]) at Weeks 26, 52 and 78. No overall differences were observed among the treatment groups throughout the duration of the study. No impact of switching patients during treatment period II from Prolia® to Stoboclo was observed on secondary endpoints.

5.2 PHARMACOKINETIC PROPERTIES

Following a 60 mg subcutaneous dose of denosumab, bioavailability was 61% and maximum serum denosumab concentrations (C_{max}) of 6 µg/mL (range 1-17 µg/mL) occurred in 10 days (range 2-28 days). After C_{max}, 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 of patients had no measurable amounts of denosumab detected at 6 months post-dose.

No accumulation or change in denosumab pharmacokinetics over time was observed upon subcutaneous multiple-dosing of 60 mg once every 6 months. Denosumab pharmacokinetics was not affected by the formation of binding antibodies to denosumab and was similar in men and women.

Pharmacokinetic analysis was performed to evaluate the effects of demographic characteristics. This analysis showed no notable difference in pharmacokinetics with age (28 to 87 years), race or body weight (36 to140 kg).

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

Immunogenicity

In clinical studies, no neutralising antibodies for denosumab have been observed. 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.

Paediatric population

The pharmacokinetic profile has not been assessed in those ≤ 18 years.

Elderly

The pharmacokinetics of denosumab was not affected by age (28 to 87 years).

Impaired hepatic function

The pharmacokinetic profile has not been assessed in patients with impaired hepatic function.

Impaired renal function

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 (see section 4.4, Hypocalcaemia and section 4.2, Renal impairment).

Comparability of Stoboclo with Prolia

The pharmacokinetic (PK) comparability of Stoboclo was demonstrated in a Phase I study in 154 healthy subjects comparing Stoboclo with Prolia (CT-P41 1.2). The study evaluated PK after a single dose of Stoboclo or Prolia 60 mg/1 mL as a subcutaneous injection to the upper arm via a pre-filled syringe. In this study, the primary endpoints of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max} of the Stoboclo group were found to be highly similar to those of the PROLIA group based on an ANCOVA model. healthy subjects. The 90% Confidence Intervals of the ratio of the geometric LS means for all primary PK endpoints were entirely contained within the pre-defined equivalence limits of 80% to 125%.

Pharmacokinetic comparability of Stoboclo with Prolia was further demonstrated in the Phase II study in 479 postmenopausal women (CT-P41 3.1). The PK parameters of C_{trough}, C_{max}, $AUC_{0\text{-}t}$, T_{max}, V_d and $t_{1/2}$ were analysed for the PK Set (Treatment Period I) and C_{trough} for the PK-Treatment Period II Subset (Treatment Period II). The mean C_{max}, $AUC_{0\text{-}t}$, T_{max}, V_d and $t_{1/2}$ of denosumab were similar between the Stoboclo and Prolia groups during Treatment Period I. The C_{trough} of denosumab showed high variability however, the mean value was generally similar between the Stoboclo and Prolia groups during Treatment Period I and II.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The carcinogenic potential of denosumab has not been evaluated in long-term animal studies. In view of the mechanism of action of denosumab, it is unlikely that the molecule would be capable of inducing tumor development or proliferation.

Carcinogenicity

The genotoxic potential of denosumab has not been evaluated. Denosumab is a recombinant protein comprised entirely of naturally occurring amino acids and contains no inorganic or synthetic organic linkers or other non-protein portions. Therefore, it is unlikely that denosumab or any of its derived fragments would react with DNA or other chromosomal material.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sorbitol
Acetic acid
Sodium acetate trihydrate
Polysorbate 20
Water for Injection (USP)

Stoboclo is a sterile, preservative-free, clear, colourless to slightly yellow solution for injection. The solution may contain trace amounts of translucent to white proteinaceous particles.

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 SHELF LIFE

54 months

If removed from the refrigerator, Stoboclo should be kept at room temperature (up to 30°C) in the original container and must be used within 63 days. If unused, STOBOCLO may be returned to the refrigerator for up to 3 days, after which it must be discarded.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

It is recommended to store the pre-filled syringe in a refrigerator at 2° to 8°C in the original carton. Do not freeze. Protect from direct light. Do not excessively shake the pre-filled syringe. Do not expose to temperatures above 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Pre-filled syringe with automatic needle guard.

Pack size of one.

The pre-filled syringe with automatic needle guard is not made with natural rubber latex.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Celltrion Healthcare New Zealand

Level 1, 46 Stanley Street, Parnell,
Auckland, 1010, New Zealand

Phone: 0800 838 8900

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 30/10/2025

10 DATE OF REVISION

27 March 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
6.3, 6.4	Change to in-use shelf-life and storage condition