PROLIA® (denosumab) Brief Prescribing Information :
Please refer to the Summary of Product Characteristics before prescribing **PROLIA®. Pharmaceutical Form**: Prolia 60 mg (denosumab) solution for injection in pre-filled syringe. Clear, colourless to slightly yellow solution**. Clinical particulars. Therapeutic indications** Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women Prolia significantly reduces the risk of vertebral, non-vertebral and hip fractures.Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures. Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture **Posology and method of administration** Posology
The recommended dose of Prolia is 60 mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or upper arm.Patients must be adequately supplemented with calcium and vitamin D. Patients treated with Prolia should be given the package leaflet and the patient reminder card.The optimal total duration of antiresorptive treatment for osteoporosis (including both denosumab and bisphosphonates) has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of denosumab on an individual patient basis, particularly after 5 or more years of use. Elderly (age ≥ 65) No dose adjustment is required in elderly patients.Renal impairment No dose adjustment is required in patients with renal impairment. 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. Paediatric population Prolia 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 Method of administration For subcutaneous use. Administration should be performed by an individual who has been adequately trained in injection techniques. **Contraindications** Hypersensitivity to the active substance or to any of the excipients. Hypocalcaemia. **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 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) have been reported. While most cases occurred in the first few weeks of initiating therapy, it has also occurred later. 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 Prolia may develop skin infections (predominantly cellulitis) leading to hospitalisation. 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 Prolia for osteoporosis. 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 Prolia 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 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 4.8). 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 pharmaceutical agents (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 Prolia 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 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. 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. Concomitant treatment with other denosumab-containing medicinal products Patients being treated with Prolia 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 Prolia should not be used in paediatric patients (age < 18). Serious hypercalcaemia has been reported. Some clinical trial cases were complicated by acute renal injury. 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 medicinal products and other forms of interaction** In an interaction study, Prolia did not affect the pharmacokinetics of midazolam, which is metabolised by cytochrome P450 3A4 (CYP3A4). This indicates that Prolia 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. Prolia 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 Prolia. Any effects of Prolia 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 during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum. A decision on whether to abstain from breast-feeding or to abstain from therapy with Prolia should be made, taking into account the benefit of breast-feeding to the newborn/infant and the benefit of Prolia 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. **Effects on ability to drive and use machines** Prolia has no or negligible influence on the ability to drive and use

machines. **Undesirable effects** Summary of the safety profile The most common side effects with Prolia (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 have been observed in patients taking Prolia. 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), 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. Adverse reactions reported in patients with osteoporosis and breast or prostate cancer patients receiving hormone ablation: Pain in extremity, Musculoskeletal pain (Very common). Urinary tract infection, Upper respiratory tract infection, Sciatica, Constipation, Abdominal discomfort, Rash, Eczema, Alopecia (Common). Diverticulitis, Cellulitis, Ear infection, Lichenoid drug eruptions (Uncommon).Drug hypersensitivity, Anaphylactic reaction, Hypocalcaemia, Osteonecrosis of the jaw, Atypical femoral fractures (Rare). Hypersensitivity vasculitis (Very rare). Osteonecrosis of the external auditory canal (Not known). 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 Prolia 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 resulting in hospitalisation, life-threatening events, and fatal cases have been reported, predominantly in patients at increased risk of hypocalcaemia receiving Prolia, 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. 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 Prolia groups: in postmenopausal women with osteoporosis (placebo [1.2%, 50 out of 4,041] versus Prolia [1.5%, 59 out of 4,050]); in men with osteoporosis (placebo [0.8%, 1 out of 120] versus Prolia [0%, 0 out of 120]); in breast or prostate cancer patients receiving hormone ablation (placebo [1.7%, 14 out of 845] versus Prolia [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 Prolia. 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 Prolia (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. Thirteen of these ONJ cases occurred in postmenopausal women with osteoporosis during the phase III clinical trial extension following treatment with Prolia for up to 10 years. Incidence of ONJ was 0.04% at 3 years, 0.06% at 5 years and 0.44% at 10 years of Prolia treatment. The risk of ONJ increased with duration of exposure to Prolia. Atypical fractures of the femur In the osteoporosis clinical trial program, atypical femoral fractures were reported rarely in patients treated with Prolia. 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 Prolia. Musculoskeletal pain Musculoskeletal pain, including severe cases, has been reported in patients receiving Prolia 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. 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 Prolia should not be used in paediatric patients (age < 18). Serious hypercalcaemia has been reported . 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. 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 to their local representative. **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. **Special precautions for storage** Store in a refrigerator (2°C – 8°C). Do not freeze. Keep the container in the outer carton in order to protect from light. **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. **Legal category** POM **Administrative information: Marketing authorization holder** Amgen Europe B.V. Minervum 7061 -4817 ZK Breda The Netherlands. **Local Marketing Authorization Numbers** 17-457-13 **DATE OF REVISION OF THE TEXT** January 2024 **Local representive in Saudi Arabia:** : Cigalah Group of Companies. Address: Office Number 606&607, 6th floor, Al Akariya Building Number 2, Olaya Street, Riyadh, PIN 11533, Kingdom of Saudi Arabia.Tel: 00966114191471

Any suspected adverse reactions should be reported immediately to Amgen in accordance with local spontaneous reporting requirements. Amgen Fax: +966 11 2799301 or send to mailbox: Safety-MEA@amgen.com and/or National Pharmacovigilance Centre (NPC), Email: npc.drug@sfda.gov.sa , Fax: +966-11-2057662 ,SFDA Call Center 19999, website: http://ade.sfda.gov.sa