To be sold by retail on the prescription of an Endocrinologist, Rheumatologist and Orthopedicians only 8101996-9093

Denosumab 60 mg/mL (r-DNA origin) in prefilled syringe
DENSUCOR

1. GENERIC NAME
Denosumab 60 mg/mL (r-DNA origin) in prefilled syringe
2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 1.0 mL single dose pre-filled syringe contains-

Denosumab Drug Substance (r-DNA Origin) In-house	60 mg
Sorbitol (JP, Ph.Eur, BP, NF, IP)	47.0 mg (4.7%)
Glacial acetic acid (Ph.Eur, BP, IP, JP, USP)	1.0 mg (17 mM)
Polysorbate 20 (BP, EP, IP, JP, NF)	0.1 mg (0.01 %)
Sodium hydroxide (IP, USP, BP, EP, JP, NF)	q.s. to adjust pH to 5.2
Water for injection (IP, USP)	q.s. to 1 mL

Denosumab is a human monoclonal IgG2 antibody produced in a mammalian cell line (Chinese hamster ovary cells) by recombinant DNA technology.
<u>Excipient with known effect</u>
This medicine contains 47 mg sorbitol in each mL of solution.
3. DOSAGE FORM AND STRENGTH
Denosumab 60 mg solution for injection in pre-filled syringe.
Clear, colourless to slightly yellow solution.
4. CLINICAL PARTICULARS
4.1 Therapeutic indications
1. Treatment of osteoporosis in postmenopausal women.
2. Treatment to increase bone mass in men with osteoporosis at high risk of fracture.
3. Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer.
4. Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.
5. Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture.

4.2 Posology and method of administration
The recommended dose is 60 mg denosumab 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.
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 (see section 4.4).
Elderly (age ≥ 65)
No dose adjustment is required in elderly patients.
Renal impairment
No dose adjustment is required in patients with renal impairment (see section 4.4 for recommendations relating to monitoring of calcium).
No data is available in patients with long-term systemic glucocorticoid therapy and severe renal impairment (GFR < 30 ml/min).
Hepatic impairment
The safety and efficacy of denosumab have not been studied in patients with hepatic impairment (see section 5.2).
Pediatric population
Denosumab is not recommended in pediatric patients (age < 18) as the safety and efficacy of denosumab in these patients have not been established. Inhibition of RANK/RANK ligand (RANKL) in animal studies has been coupled to inhibition of bone growth and lack of tooth eruption (see section 5.3).
<u>Method of administration</u>
For subcutaneous use.
Administration should be performed by an individual who has been adequately trained in injection techniques.
4.3 Contraindications
- Hypersensitivity to the active substance or to any of the excipients listed in section 2.
- Hypocalcaemia (see section 4.4).

4.4 Special warnings and precautions for use
<u>Calcium and vitamin D supplementation</u>
Adequate intake of calcium and vitamin D is important in all patients.
<u>Precautions for use</u>
Hypocalcaemia
It is important to identify patients at risk for hypocalcaemia. Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Clinical monitoring of calcium levels is recommended before each dose and, in patients predisposed to hypocalcaemia within two weeks after the initial dose. If any patient presents with suspected symptoms of hypocalcaemia during treatment (see section 4.8 for symptoms) calcium levels should be measured. Patients should be encouraged to report symptoms indicative of hypocalcaemia.
In the post-marketing setting, severe symptomatic hypocalcaemia (including fatal cases) has been reported (see section 4.8), with most cases occurring in the first weeks of initiating therapy, but it can occur 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. Adequate intake of calcium, vitamin D and regular monitoring of calcium is especially important in these patients, see above.
Skin infections
Patients receiving denosumab may develop skin infections (predominantly cellulitis) leading to hospitalisation (see section 4.8). Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.
Osteonecrosis of the Jaw (ONJ)
ONJ has been reported rarely in patients receiving denosumab for osteoporosis (see section 4.8).
The start of treatment/new treatment course should be delayed in patients with unhealed open soft tissue lesions in the mouth. A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with denosumab in patients with concomitant risk factors.
The following risk factors should be considered when evaluating a patient's risk of developing ONJ:
- potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy.
- cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking.
- concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck.
- poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures e.g. tooth extractions.

All patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling or non-healing of sores or discharge during treatment with denosumab. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to denosumab administration.
The management plan of the patients who develop ONJ should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in ONJ. Temporary interruption of treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.
Osteonecrosis of the external auditory canal
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 medicinal products (e.g. bisphosphonates, glucocorticoids, proton pump inhibitors). These events have also occurred without antiresorptive therapy. Similar fractures reported in association with bisphosphonates are often bilateral; therefore, the contralateral femur should be examined in denosumab-treated patients who have sustained a femoral shaft fracture. Discontinuation of denosumab 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 (see section 4.2).
Concomitant treatment with other denosumab-containing medicinal products
Patients being treated with denosumab 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).
Dry natural rubber
The needle cover of the pre-filled syringe comprised of synthetic polyisoprene (rigid needle shield 4800GS) which is latex free and non – cytotoxic.
Warnings for excipients
This medicine contains 47 mg (4.7 %) 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'.
4.5 Drug interactions
In an interaction study, denosumab did not affect the pharmacokinetics of midazolam, which is metabolised by cytochrome P450 3A4 (CYP3A4). This indicates that denosumab should not alter the pharmacokinetics of medicinal products metabolised by CYP3A4.
There are no clinical data on the co-administration of denosumab and hormone replacement therapy (estrogen), 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).
4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)
<u>Pregnant women</u>
There are no or limited amount of data from the use of denosumab in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).
Denosumab 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 denosumab. Any effects of densoumab 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.
<u>Lactating women</u>
It is unknown whether denosumab is excreted in human milk. In genetically engineered mice in which RANKL has been turned off by gene removal (a "knockout mouse"), studies suggest absence of RANKL (the target of denosumab see section 5.1) during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum (see section 5.3). 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.
<u>Fertility</u>
No data are available on the effect of denosumab on human fertility. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3)
<u>Paediatric patients</u>
Denosumab is not recommended in pediatric patients younger than age 4 years because of the high rates of skeletal growth and the potential for denosumab to negatively affect long-bone growth and dentition. The safety and effectiveness of denosumab in pediatric patients have not been established.
Treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition. In neonatal rats, inhibition of RANKL (the target of denosumab therapy) with a construct of osteoprotegerin bound to Fc (OPG-Fc) at doses ≤ 10 mg/kg was associated with inhibition of bone growth and tooth eruption. Adolescent primates treated with denosumab at doses 10 and 50 times (10 and 50 mg/kg dose) higher than the recommended human dose of 60 mg administered every 6 months, based on body weight (mg/kg), had abnormal growth plates, considered to be consistent with the pharmacological activity of denosumab.
<u>Geriatric patients</u>
Of the total number of patients in clinical studies of denosumab, 9943 patients (76%) were ≥ 65 years old, while 3576 (27%) were ≥ 75 years old. Of the patients in the osteoporosis study in men, 133 patients (55%) were ≥ 65 years old, while 39 patients (16%) were ≥ 75 years old. Of the patients in the glucocorticoid-induced osteoporosis study, 355 patients (47%) were ≥ 65 years old, while 132 patients (17%) were ≥ 75 years old. No overall differences in safety or efficacy were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.
4.7 Effects on ability to drive and use machines
Denosumab has no or negligible influence on the ability to drive and use machines.
4.8 Undesirable effects
<u>Summary of the safety profile</u>
The most common side effects with denosumab (seen in more than one patient in ten) are musculoskeletal pain and pain in the extremity. Uncommon cases of cellulitis, rare cases of hypocalcaemia, hypersensitivity, osteonecrosis of the jaw and atypical femoral fractures have been observed in patients taking denosumab.
In an Indian phase III clinical study in women with postmenopausal osteoporosis, common (i.e. ≥ 1 %) treatment emergent adverse events (TEAEs) reported were nausea (1.7%), aspartate aminotransferase increased (1.7%), compression fracture (1.7%), nasopharyngitis (1.7%), myalgia (2.6%), gastritis (2.6%), pain in extremity (2.6%), blood creatinine increased (2.6%), iron deficiency anaemia (2.6%), pyrexia (3.4%), back pain (4.3%) and upper respiratory tract infection (5.2%).
<u>Tabulated list of adverse reactions</u>
The data in Table 1 below describe adverse reactions reported from Phase II and III clinical trials in patients with osteoporosis and breast or prostate cancer patients receiving hormone ablation; and/or spontaneous reporting as well as Indian phase III clinical study.
The following convention has been used for the classification of the adverse reactions (see table 1): very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping and system organ class, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions reported in patients with osteoporosis and breast or prostate cancer patients receiving hormone ablation

MedDRA system organ class	Frequency category	Adverse reactions
Infections and infestations	Common Common# Common# Uncommon Uncommon Uncommon	Urinary tract infection Upper respiratory tract infection Nasopharyngitis Diverticulitis Cellulitis Ear infection
Immune system disorders	Rare Rare	Drug hypersensitivity Anaphylactic reaction1
Metabolism and nutrition disorders	Rare	Hypocalcaemia
Nervous system disorders	Common	Sciatica
Gastrointestinal disorders	Common# Common Common Common# Common#	Nausea Constipation Abdominal discomfort Gastritis Aspartate aminotransferase increased
Skin and subcutaneous tissue disorders	Common Common Uncommon Uncommon Very rare	Rash Eczema Alopecia Lichenoid drug eruption Hypersensitivity vasculitis
Musculoskeletal and connective tissue disorders	Very common# Very common Common# Common# Common# Rare Rare Not Known	Pain in extremity Musculoskeletal pain Myalgia Back pain Compression fracture Osteonecrosis of the jaw Atypical femoral fractures Osteonecrosis of the external auditory canal
General disorders and administration site conditions	Common#	Pyrexia

#frequency of adverse events reported as per Indian phase III clinical study.
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.
<u>Description of selected adverse reactions</u>
Hypocalcaemia
In two phase III placebo-controlled clinical trials in postmenopausal women with osteoporosis, approximately 0.05% (2 out of 4,050) of patients had declines of serum calcium levels (less than 1.88 mmol/l) following denosumab administration. Declines of serum calcium levels (less than 1.88 mmol/l) were not reported in either the two phase III placebo-controlled clinical trials in patients receiving hormone ablation or the phase III placebo-controlled clinical trial in men with osteoporosis. However, in Indian phase III clinical study 5.2% (6 out of 116) patients had declines of serum calcium levels.
In the post-marketing setting, rare cases of severe symptomatic hypocalcaemia have been reported predominantly in patients at increased risk of hypocalcaemia receiving denosumab, with most cases occurring in the first weeks of initiating therapy. Examples of the clinical manifestations of severe symptomatic hypocalcaemia have included QT interval prolongation, tetany, seizures and altered mental status (see section 4.4). Symptoms of hypocalcaemia in denosumab clinical studies included paraesthesias or muscle stiffness, twitching, spasms and muscle cramps.
Skin infections
In phase III placebo-controlled clinical trials, the overall incidence of skin infections was similar in the placebo and the denosumab groups: in postmenopausal women with osteoporosis (placebo [1.2%, 50 out of 4,041] versus denosumab [1.5%, 59 out of 4,050]); in men with osteoporosis (placebo [0.8%, 1 out of 120] versus denosumab [0%, 0 out of 120]); in breast or prostate cancer patients receiving hormone ablation (placebo [1.7%, 14 out of 845] versus denosumab [1.4%, 12 out of 860]). Skin infections leading to hospitalisation were reported in 0.1% (3 out of 4,041) of postmenopausal women with osteoporosis receiving placebo versus 0.4% (16 out of 4,050) of women receiving denosumab. These cases were predominantly cellulitis. Skin infections reported as serious adverse reactions were similar in the placebo (0.6%, 5 out of 845) and the denosumab (0.6%, 5 out of 860) groups in the breast and prostate cancer studies.
Osteonecrosis of the jaw
ONJ has been reported rarely, in 16 patients, in clinical trials in osteoporosis and in breast or prostate cancer patients receiving hormone ablation including a total of 23,148 patients (see section 4.4). Thirteen of these ONJ cases occurred in postmenopausal women with osteoporosis during the phase III clinical trial extension following treatment with denosumab for up to 10 years. Incidence of 8 ONJ was 0.04% at 3 years, 0.06% at 5 years and 0.44% at 10 years of denosumab treatment. The risk of ONJ increased with duration of exposure to denosumab.
Atypical fractures of the femur
In the osteoporosis clinical trial program, atypical femoral fractures were reported rarely in patients treated with denosumab (see section 4.4).
Diverticulitis
In a single phase III placebo-controlled clinical trial in patients with prostate cancer receiving ADT an imbalance in diverticulitis adverse events was observed (1.2% denosumab, 0% placebo). The incidence of diverticulitis was comparable between treatment groups in postmenopausal women or men with osteoporosis and in women undergoing aromatase inhibitor therapy for non-metastatic breast cancer.
Drug-related hypersensitivity reactions
In the post-marketing setting, rare events of drug-related hypersensitivity, including rash, urticaria, facial swelling, erythema, and anaphylactic reactions have been reported in patients receiving Denosumab.
Musculoskeletal pain
Musculoskeletal pain, including severe cases, has been reported in patients receiving Denosumab in the post-marketing setting. In clinical trials, musculoskeletal pain was very common in both denosumab and placebo groups. Musculoskeletal pain leading to discontinuation of study treatment was uncommon.
Lichenoid drug eruptions
Lichenoid drug eruptions (e.g. lichen planus-like reactions) have been reported in patients in the postmarketing setting.
<u>Other special populations</u>
Renal impairment
In clinical studies, patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis were at greater risk of developing hypocalcaemia in the absence of calcium supplementation. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis (see section 4.4).
<u>Reporting of side effects</u>
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. Report suspected adverse reactions via any point of contact available at <u>www.torrentpharma.com.</u>
4.9 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.
5. PHARMACOLOGICAL PROPERTIES
5.1 Mechanism of action
Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL, preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone.
5.2 Pharmacodynamic properties
Pharmacotherapeutic group: Drugs for treatment of bone diseases – Other drugs affecting bone structure and mineralisation, ATC code: M05BX04.
Denosumab treatment rapidly reduced the rate of bone turnover, reaching a nadir for the bone resorption marker serum type 1 C-telopeptides (CTX) (85% reduction) by 3 days, with reductions maintained over the dosing interval. At the end of each dosing interval, CTX reductions were partially attenuated from maximal reduction of ≥ 87% to approximately ≥ 45% (range 45-80%), reflecting the reversibility of Denosumab's effects on bone remodelling once serum levels diminish. These effects were sustained with continued treatment. Bone turnover markers generally reached pre-treatment levels within 9 months after the last dose. Upon re-initiation, reductions in CTX by denosumab were similar to those observed in patients initiating primary denosumab treatment.
<u>Immunogenicity</u>
In an Indian clinical study, treatment emergent anti-denosumab antibodies were detected in 1.89% patients (2 out of 116) in denosumab group (i.e. test group).
<u>Clinical efficacy and safety in postmenopausal women with osteoporosis</u>
Efficacy and safety of denosumab administered once every 6 months for 3 years were investigated in postmenopausal women (7,808 women aged 60-91 years, of which 23.6% had prevalent vertebral fractures) with baseline bone mineral density (BMD) T-scores at the lumbar spine or total hip between –2.5 and –4.0 and a mean absolute 10-year fracture probability of 18.60% (deciles: 7.9-32.4%) for major osteoporotic fracture and 7.22% (deciles: 1.4-14.9%) for hip fracture. Women with other diseases or on therapies that may affect bone were excluded from this study. Women received calcium (at least 1,000 mg) and vitamin D (at least 400 IU) supplementation daily.
Effect on vertebral fractures
Denosumab significantly reduced the risk of new vertebral fractures at 1, 2 and 3 years (p < 0.0001) (see table 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)
	Placebo n = 3,906	Denosumab n = 3,902		
0-1 year	2.2	0.9	1.4 (0.8, 1.9)	61 (42, 74)**
0-2 years	5.0	1.4	3.5 (2.7, 4.3)	71 (61, 79)**
0-3 years	7.2	2.3	4.8 (3.9, 5.8)	68 (59, 74)*

*p < 0.0001, **p < 0.0001 – exploratory analysis
Effect on hip fractures
Denosumab demonstrated a 40% relative reduction (0.5% absolute risk reduction) in the risk of hip fracture over 3 years (p < 0.05). The incidence of hip fracture was 1.2% in the placebo group compared to 0.7% in the denosumab group at 3 years. In a post-hoc analysis in women > 75 years, a 62% relative risk reduction was observed with denosumab (1.4% absolute risk reduction, p < 0.01).
Effect on all clinical fractures
Denosumab significantly reduced fractures across all fracture types/groups (see table 3).

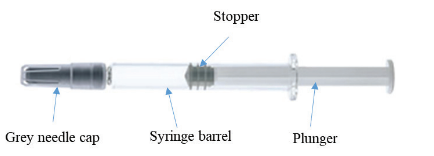
Table 3. The effect of denosumab on the risk of clinical fractures over 3 years

	Proportion of women with fracture (%)[+]		Absolute risk reduction (%) (95% CI)	Relative risk reduction (%) (95% CI)
	Placebo n = 3,906	Denosumab n = 3,902		
Any clinical fracture[1]	10.2	7.2	2.9 (1.6, 4.2)	30 (19, 41)***
Clinical vertebral fracture	2.6	0.8	1.8 (1.2, 2.4)	69 (53, 80)***
Non-vertebral fracture[2]	8.0	6.5	1.5 (0.3, 2.7)	20 (5, 33)**
Major non-vertebral fracture[3]	6.4	5.2	1.2 (0.1, 2.2)	20 (3, 34)*
Major osteoporotic fracture[4]	8.0	5.3	2.7 (1.6, 3.9)	35 (22, 45)***

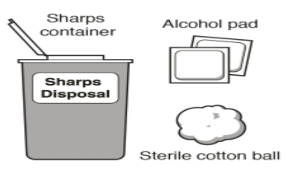
*p ≤ 0.05; **p = 0.0106 *(secondary endpoint included in multiplicity adjustment)*, ***p ≤ 0.0001
[+] Event rates based on Kaplan-Meier estimates at 3 years.
[1] Includes clinical vertebral fractures and non-vertebral fractures.
[2] Excludes those of the vertebrae, skull, facial, mandible, metacarpus, and finger and toe phalanges.
[3] Includes pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip.
[4] Includes clinical vertebral, hip, forearm, and humerus fractures, as defined by the WHO.
In women with baseline femoral neck BMD ≤ -2.5, denosumab reduced the risk of non-vertebral fracture (35% relative risk reduction, 4.1% absolute risk reduction, p < 0.001, exploratory analysis).
The reduction in the incidence of new vertebral fractures, hip fractures and non-vertebral fractures by denosumab over 3 years were consistent regardless of the 10-year baseline fracture risk.
Effect on bone mineral density
Denosumab significantly increased BMD at all clinical sites measured, versus placebo at 1, 2 and 3 years. Denosumab increased BMD by 9.2% at the lumbar spine, 6.0% at the total hip, 4.8% at the femoral neck, 7.9% at the hip trochanter, 3.5% at the distal 1/3 radius and 4.1% at the total body over 3 years (all p < 0.0001).
In clinical studies examining the effects of discontinuation of denosumab, BMD returned to approximately pre-treatment levels and remained above placebo within 18 months of the last dose. These data indicate that continued treatment with Denosumab is required to maintain the effect of the medicinal product. Re-initiation of Denosumab resulted in gains in BMD similar to those when Denosumab was first administered.
Open-label extension study in the treatment of postmenopausal osteoporosis
A total of 4,550 women (2,343 Denosumab & 2,207 placebo) who missed no more than one dose of investigational product in the pivotal study described above and completed the month 36 study visit agreed to enrol in a 7-year, multinational, multicentre, open-label, single-arm extension study to evaluate the long-term safety and efficacy of Denosumab. All women in the extension study were to receive denosumab 60 mg every 6 months, as well as daily calcium (at least 1 g) and vitamin D (at least 400 IU). A total of 2,626 subjects (58% of the women included in the extension study i.e. 34% of the women included in the pivotal study) completed the extension study.
In patients treated with denosumab for up to 10 years, BMD increased from the pivotal study baseline by 21.7% at the lumbar spine, 9.2% at the total hip, 9.0% at the femoral neck, 13.0% at the trochanter and 2.8% at the distal 1/3 radius. The mean lumbar spine BMD T-score at the end of the study was -1.3 in patients treated for 10 years.
Fracture incidence was evaluated as a safety endpoint but efficacy in fracture prevention cannot be estimated due to high number of discontinuations and open-label design. The cumulative incidence of new vertebral and non-vertebral fractures were approximately 6.8% and 13.1% respectively, in patients who remained on denosumab treatment for 10 years (n = 1,278). Patients who did not complete the study for any reason had higher on-treatment fracture rates.
Thirteen adjudicated cases of osteonecrosis of the jaw (ONJ) and two adjudicated cases of atypical fractures of the femur occurred during the extension study.
<u>Clinical efficacy and safety in men with osteoporosis</u>
Efficacy and safety of denosumab once every 6 months for 1 year were investigated in 242 men aged 31-84 years. Subjects with an eGFR < 30 mL/min/1.73 m^2 were excluded from the study. All men received calcium (at least 1,000 mg) and vitamin D (at least 800 IU) supplementation daily.
The primary efficacy variable was percent change in lumbar spine BMD, fracture efficacy was not evaluated. Denosumab significantly increased BMD at all clinical sites measured, relative to placebo at 12 months: 4.8% at lumbar spine, 2.0% at total hip, 2.2% at femoral neck, 2.3% at hip trochanter, and 0.9% at distal 1/3 radius (all p < 0.05). Denosumab increased lumbar spine BMD from baseline in 94.7% of men at 1 year. Significant increases in BMD at lumbar spine, total hip, femoral neck and hip trochanter were observed by 6 months (p < 0.0001).
<u>Bone histology in postmenopausal women and men with osteoporosis</u>
Bone histology was evaluated in 62 postmenopausal women with osteoporosis or with low bone mass who were either naïve to osteoporosis therapies or had transitioned from previous alendronate therapy following 1-3 years treatment with denosumab. Fifty nine women participated in the bone biopsy sub-study at month 24 (n = 41) and/or month 84 (n = 22) of the extension study in postmenopausal women with osteoporosis. Bone histology was also evaluated in 17 men with osteoporosis following 1 year treatment with denosumab. Bone biopsy results showed bone of normal architecture and quality with no evidence of mineralisation defects, woven bone or marrow fibrosis. Histomorphometry findings in the extension study in postmenopausal women with osteoporosis showed that the antiresorptive effects of denosumab, as measured by activation frequency and bone formation rates, were maintained over time.
<u>Clinical efficacy and safety in patients with bone loss associated with androgen deprivation</u>
Efficacy and safety of denosumab once every 6 months for 3 years were investigated in men with histologically confirmed non-metastatic prostate cancer receiving ADT (1,468 men aged 48-97 years) who were at increased risk of fracture (defined as > 70 years, or < 70 years with a BMD T-score at the lumbar spine, total hip, or femoral neck < -1.0 or a history of an osteoporotic fracture.) All men received calcium (at least 1,000 mg) and vitamin D (at least 400 IU) supplementation daily.
Denosumab significantly increased BMD at all clinical sites measured, relative to treatment with placebo at 3 years: 7.9% at the lumbar spine, 5.7% at the total hip, 4.9% at the femoral neck, 6.9% at the hip trochanter, 6.9% at the distal 1/3 radius and 4.7% at the total body (all p < 0.0001). In a prospectively planned exploratory analysis, significant increases in BMD were observed at the lumbar spine, total hip, femoral neck and the hip trochanter 1 month after the initial dose.
Denosumab demonstrated a significant relative risk reduction of new vertebral fractures: 85% (1.6% absolute risk reduction) at 1 year, 69% (2.2% absolute risk reduction) at 2 years and 62% (2.4% absolute risk reduction) at 3 years (all p < 0.01).
<u>Clinical efficacy and safety in patients with bone loss associated with adjuvant aromatase inhibitor therapy</u>
Efficacy and safety of denosumab once every 6 months for 2 years were investigated in women with non-metastatic breast cancer (252 women aged 35-84 years) and baseline BMD T-scores between -1.0 to -2.5 at the lumbar spine, total hip or femoral neck. All women received calcium (at least 1,000 mg) and vitamin D (at least 400 IU) supplementation daily.
The primary efficacy variable was percent change in lumbar spine BMD, fracture efficacy was not evaluated. Denosumab significantly increased BMD at all clinical sites measured, relative to treatment with placebo at 2 years: 7.6% at lumbar spine, 4.7% at total hip, 3.6% at femoral neck, 5.9% at hip trochanter, 6.1% at distal 1/3 radius and 4.2% at total body (all p < 0.0001).
<u>Treatment of bone loss associated with systemic glucocorticoid therapy</u>
Efficacy and safety of Denosumab were investigated in 795 patients (70% women and 30% men) aged 20 to 94 years treated with ≥ 7.5 mg daily oral prednisone (or equivalent).
Two subpopulations were studied: glucocorticoid-continuing (≥ 7.5 mg daily prednisone or its equivalent for ≥ 3 months prior to study enrolment; n = 505) and glucocorticoid-initiating (≥ 7.5 mg daily prednisone or its equivalent for < 3 months prior to study enrolment; n = 290). Patients were randomised (1:1) to receive either denosumab 60 mg subcutaneously once every 6 months or oral risedronate 5 mg once daily (active control) for 2 years. Patients received calcium (at least 1,000 mg) and vitamin D (at least 800 IU) supplementation daily.
Effect on Bone Mineral Density (BMD)
In the glucocorticoid-continuing subpopulation, denosumab demonstrated a greater increase in lumbar spine BMD compared to risedronate at 1 year (denosumab 3.6%, risedronate 2.0%; p < 0.001) and 2 years (denosumab 4.5%, risedronate 2.2%; p < 0.001). In the glucocorticoid-initiating subpopulation, denosumab demonstrated a greater increase in lumbar spine BMD compared to risedronate at 1 year (denosumab 3.1%, risedronate 0.8%; p < 0.001) and 2 years (denosumab 4.6%, risedronate 1.5%; p < 0.001).
In addition, denosumab demonstrated a significantly greater mean percent increase in BMD from baseline compared to risedronate at the total hip, femoral neck, and hip trochanter.
The study was not powered to show a difference in fractures. At 1 year, the subject incidence of new radiological vertebral fracture was 2.7% (denosumab) versus 3.2% (risedronate). The subject incidence of non-vertebral fracture was 4.3% (denosumab) versus 2.5% (risedronate). At 2 years, the corresponding numbers were 4.1% versus 5.8% for new radiological vertebral fractures and 5.3% versus 3.8% for non-vertebral fractures. Most of the fractures occurred in the GC-C subpopulation.

<u>Clinical efficacy of biosimilar denosumab (DENSUCOR) in postmenopausal women with osteoporosis in Indian clinical study</u>
The efficacy and safety of biosimilar denosumab in the treatment of postmenopausal osteoporosis was demonstrated in a randomized, double-blind, active-controlled, phase III trial. Women aged between 50 to 80 years of age with BMD T-score ≤ 2.5 at either the lumbar spine or total hip were included in this study. Women with other diseases (such as rheumatoid arthritis, osteomalacia, osteogenesis imperfecta, and Paget's disease) or on therapies that affect bone were excluded from this study. The 177 enrolled women were aged 56 to 71 years with a mean age of 63.4 years. Women were randomized in 2:1 ratio (i.e. 116 subjects in Biosimilar Denosumab and 61 subjects in Innovator Denosumab-Prolia® arm) to enter into the treatment period of 12 months. Patients received subcutaneous injections of either Biosimilar Denosumab or Innovator Denosumab-Prolia® once every 6 months. All women received at least 1000 mg calcium and 500 IU vitamin D supplementation daily.
The primary efficacy variable was percent change in Lumbar and Femoral neck Bone Mineral Density (BMD) from baseline to Month 6 and Month 12 of treatment. Secondary efficacy variables included the change in PD biomarkers (serum type 1 C-telopeptide [CTX] and serum Procollagen I N-terminal Propeptide [P1NP]) at months 1, 6 and 12 of treatment.
Out of 177 subjects who were enrolled in the study, 31 subjects (i.e. 15 subjects in Biosimilar Denosumab arm and 16 subjects in Innovator Denosumab-Prolia® arm) were considered for PK sub-study at baseline visit in-order to have 30 evaluable subjects in PK sub-study.
Effect on BMD at lumbar spine and at femoral neck (per protocol population)
There was significant improvement observed in percentage change from baseline to at 12 months in BMD at lumbar spine in both treatment groups (p- value<.0001). No significant difference (p=0.9468) in percentage change in BMD at lumbar spine was observed between Test and Reference at 12 months. A between-treatment difference of 0.1051 with 95% CI (-3.0042;3.2144) in LSM percentage change in BMD from baseline to 12 months at lumbar spine was observed between Biosimilar Denosumab and Innovator Denosumab - Prolia® group.
There was significant improvement observed in percentage change from baseline to 12 months in BMD at femoral neck in both treatment groups (p- value <0.01). No significant difference (p=0.6231) in percentage change in BMD at femoral neck was observed between Test and Reference at 12 months. A between-treatment difference of -0.8484 with 95% CI (-4.2532;2.5565) in percentage change in BMD from baseline to 12 months at femoral neck was observed between Biosimilar Denosumab and Innovator Denosumab - Prolia® group.
Since the lower limit of the confidence interval was higher than -15% (the non-inferiority margin specified in the protocol), therefore, non-inferiority of the test arm compared to reference arm is demonstrated for lumbar spine and femoral neck.
Effects on serum PINP & CTX levels at 1 and 6 months (per protocol population)
There was significant reduction observed in mean serum PINP levels from baseline to Month 1, 6 and 12 in both treatment groups (p- value<.0001). There was no significant reduction observed in CTX levels at 1 and 6 months from baseline. There was statistically significant difference observed in mean change from baseline to Month 12 in the Serum CTX in both treatment groups (p- value 0.0009 for test product, p value 0.0010 for reference product). However, there was no significant difference noted between the two treatment groups in reductions of serum PINP and CTX levels from baseline at 1, 6 and 12 months. Thus both the treatment groups were comparable.
<u>Paediatric population</u>
See section 4.2 for information on paediatric use.
5.3 Pharmacokinetic properties
<u>Absorption</u>
Following subcutaneous administration of 60 mg dose, exposure based on AUC was 78% as compared to intravenous administration at the same dose 13 level. In an Indian pharmacokinetic study at 60 mg subcutaneous dose, maximum serum denosumab concentrations (Cmax) of ~5.9 mcg/mL (range 2.3-9.5 µg/mL) occurred in ~10 days.
<u>Biotransformation</u>
Denosumab is composed solely of amino acids and carbohydrates as native immunoglobulin and is unlikely to be eliminated via hepatic metabolic mechanisms. Its metabolism and elimination are expected to follow the immunoglobulin clearance pathways, resulting in degradation to small peptides and individual amino acids.
<u>Elimination</u>
After Cmax, serum levels declined with a half-life of 26 days (range 6-52 days) over a period of 3 months (range 1.5-4.5 months). Fifty-three percent (53%) of patients had no measurable amounts of Denosumab detected at 6 months post-dose.
No accumulation or change in Denosumab pharmacokinetics with time was observed upon subcutaneous multiple-dosing of 60 mg once every 6 months. Denosumab pharmacokinetics were not affected by the formation of binding antibodies to Denosumab and were similar in men and women. Age (28-87 years), race and disease state (low bone mass or osteoporosis; prostate or breast cancer) do not appear to significantly affect the pharmacokinetics of Denosumab.
A trend was observed between higher body weight and lower exposure based on AUC and Cmax. However, the trend is not considered clinically important, since pharmacodynamic effects based on bone turnover markers and BMD increases were consistent across a wide range of body weight.
<u>Linearity/non-linearity</u>
In dose ranging studies, Denosumab exhibited non-linear, dose-dependent pharmacokinetics, with lower clearance at higher doses or concentrations, but approximately dose-proportional increases in exposures for doses of 60 mg and greater.
<u>Renal impairment</u>
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
<u>Hepatic impairment</u>
No specific study in patients with hepatic impairment was performed. In general, monoclonal antibodies are not eliminated via hepatic metabolic mechanisms. The pharmacokinetics of Denosumab is not expected to be affected by hepatic impairment.
<u>Paediatric population</u>
The pharmacokinetic profile in paediatric populations has not been assessed
6. Nonclinical properties
6.1 Animal Toxicology or Pharmacology
Denosumab at the dose level of 62 mg/kg body weight/ week of Sprague-Dawley rats had no noteworthy effects on general health of the animals, body weight, net body weight gains, feed consumption, immunogenicity, haematology, clinical chemistry, serum electrolytes, urine parameters, fasting body weights, macroscopic and microscopic lesions in both the sexes at all treated groups. In view of results observed, the evaluated NOAEL is 62 mg/kg body weight/week for Enzene's Denosumab on repeated 28 subcutaneous administrations to rabbits under the test conditions and doses employed.
Denosumab at the dose levels of 31 mg/kg body weight/week of rabbits had no noteworthy effects on general health of the animals, body weight, net body weight gains, feed consumption, immunogenicity, haematology, clinical chemistry, serum electrolytes, urine parameters, fasting body weights, macroscopic and microscopic lesions in both the sexes at all treated groups. In view of results observed, the evaluated NOAEL is 31 mg/kg body weight/week for Enzene's Denosumab on repeated 28 subcutaneous administrations to rabbits under the test conditions and doses employed.
7. DESCRIPTION
Denosumab is a human monoclonal antibody (IgG2) with affinity and specificity for human RANKL (receptor activator of nuclear factor kappa-B ligand). Denosumab has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells.
Denosumab is a sterile, preservative-free, clear, colorless to pale yellow solution.
Each 1 mL single-dose prefilled syringe contains 60 mg denosumab (60 mg/mL solution), 4.7% sorbitol, 17 mM glacial acetic acid, 0.01% polysorbate 20, Water for Injection, and sodium hydroxide to adjust to a pH of 5.2.
8. PHARMACEUTICAL PARTICULARS
8.1 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products
8.2 Shelf life
Refer pack
Once removed from the refrigerator, denosumab may be stored at room temperature (up to 25°C) for up to 30 days in the original container. It must be used within this 30 days period.
8.3 Packaging information
One mL solution in a single use pre-filled syringe made from type I glass with stainless steel 27 gauge needle, with or without needle stoppered at one end with bromobutyl solid rubber plunger.
Pack size of one pre-filled syringe, presented in blistered (pre-filled syringe with or without a needle guard) or unblistered packaging (pre-filled syringe without a needle guard only).
8.4 Storage and handling instructions
Store in a refrigerator (2°C – 8°C).
Do not freeze.
Keep the container in the outer carton in order to protect from light.
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 pre-filled syringe.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements
9. PATIENT COUNSELLING INFORMATION
Hypersensitivity
Advise patients to seek prompt medical attention if signs or symptoms of hypersensitivity reactions occur. Advise patients who have had signs or symptoms of systemic hypersensitivity reactions that they should not receive denosumab.
Hypocalcemia
Advise the patient to adequately supplement with calcium and vitamin D and instruct them on the importance of maintaining serum calcium levels while receiving denosumab. Advise patients to seek prompt medical attention if they develop signs or symptoms of hypocalcemia.
Osteonecrosis of the Jaw
Advise patients to maintain good oral hygiene during treatment with denosumab and to inform their dentist prior to dental procedures that they are receiving denosumab. Patients should inform their physician or dentist if they experience persistent pain and/or slow healing of the mouth or jaw after dental surgery.
Atypical Subtrochanteric and Diaphyseal Femoral Fractures
Advise patients to report new or unusual thigh, hip, or groin pain.
Multiple Vertebral Fractures (MVF) Following Discontinuation of Denosumab Treatment
Advise patients not to interrupt denosumab therapy without talking to their physician.
Serious Infections
Advise patients to seek prompt medical attention if they develop signs or symptoms of infections, including cellulitis.
Dermatologic Adverse Reactions
Advise patients to seek prompt medical attention if they develop signs or symptoms of dermatological reactions (dermatitis, rashes, and eczema).
Musculoskeletal Pain
Inform patients that severe bone, joint, and/or muscle pain have been reported in patients taking denosumab. Patients should report severe symptoms if they develop.
Pregnancy/Nursing
Counsel females of reproductive potential to use effective contraceptive measure to prevent pregnancy during treatment and for at least 5 months after the last dose of denosumab. Advise the patient to contact their physician immediately if pregnancy does occur during these times. Advise patients not to take denosumab while pregnant or breastfeeding. If a patient wish to start breastfeeding after treatment, advise her to discuss the appropriate timing with her physician.
Schedule of Administration
Advise patients that if a dose of denosumab is missed, the injection should be administered as soon as convenient. Thereafter, schedule injections every 6 months from the date of the last injection.
10. DETAILS OF MANUFACTURER
Enzene Biosciences Ltd,
Plot No A 22, A/ 1/ 2 MIDC Chakan Industrial Area,
Phase II, Vil-Khalumbre, Taluka Khed,
Pune-410501. Maharashtra, India.
11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE
Form CT-23 Permission Number: MF/BIO/21/000062 dated 20-July-2021
License Number: MH/103810 dated 06-August-2021
12. DATE OF REVISION
NA
MARKETED BY :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.
IN/Densucor 60mg/ml/AUG-2025/01/PI

INSTRUCTIONS FOR INJECTING WITH THE DENSUCOR PRE-FILLED SYRINGE
This section contains information on how to use the DENSUCOR (60 mg/mL) pre-filled syringe. **It is important that you or your carer do not give the injection unless training from your doctor or healthcare provider has been received.** Always wash your hands before every injection. If you have questions about how to inject, please ask your doctor or healthcare provider for assistance.
Before you begin
Read all instructions thoroughly before using the pre-filled syringe.
DO NOT use the pre-filled syringe if the needle cover has been removed.
How do you use the DENSUCOR pre-filled syringe?
Your doctor has prescribed a DENSUCOR pre-filled syringe for injection into the tissue just under the skin (subcutaneous). You must inject the entire content (1 mL) of the DENSUCOR pre-filled syringe and it should be injected once every 6 months as instructed by your doctor.
Equipment:
To give an injection, you will need:
1. A new DENSUCOR pre-filled syringe

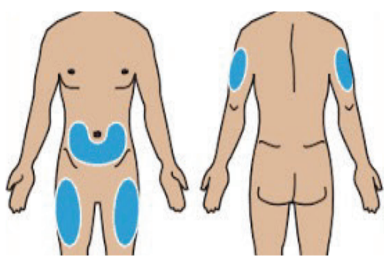


2. Alcohol wipes or similar.
3. Puncture-resistant container or sharps container for safe disposal of needle cap and used syringe



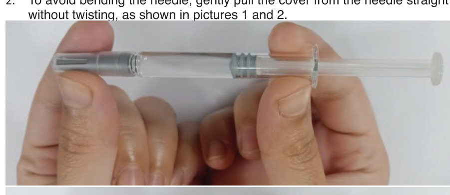
What to do before you give a subcutaneous injection of DENSUCOR
1. Remove the pre-filled syringe from the refrigerator.
   DO NOT pick up the pre-filled syringe by the plunger or needle cover. This could damage the device.
2. The pre-filled syringe may be left outside the refrigerator to reach room temperature. This will make the injection more comfortable.
   DO NOT warm it in any other way, for example, in a microwave or in hot water.
   DO NOT leave the syringe exposed to direct sunlight.
3. **DO NOT** shake the pre-filled syringe.
4. **DO NOT** remove the needle cover from the pre-filled syringe until you are ready to inject.
5. Check the expiry date on the pre-filled syringe label (EXP).
   DO NOT use it if the date has passed the last day of the month shown.
6. Check the appearance of DENSUCOR Pre filled syringe. It must be a clear, colourless to slightly yellow solution. The solution **should not be** injected if it contains particles or if it is discoloured or cloudy.
7. Find a comfortable, well-lit, clean surface and put all the equipment within reach.
8. Wash your hands thoroughly.

Where should you give the injection?
The best places to inject are the top of your thighs and the abdomen.
Your carer can also use the outer area of your upper arms.



= Injection sites

How do you give the injection?
1. Disinfect the skin by using an alcohol wipe.
2. To avoid bending the needle, gently pull the cover from the needle straight off without twisting, as shown in pictures 1 and 2.


1

2

DO NOT touch the needle or push the plunger.
3. You may notice a small air bubble in the pre-filled syringe. You do not have to remove the air bubble before injecting. Injecting the solution with the air bubble is harmless.
4. Pinch (without squeezing) the skin between your thumb and forefinger. Put the needle fully into the skin as shown by your doctor or healthcare provider
5. Push the plunger with a **slow** constant pressure, always keeping the skin pinched. Push the plunger all the way down as far as it will go to inject **all the solution.**
6. Remove the needle and let go of the skin.
7. If you notice a spot of blood you may gently dab it away with a cotton ball or tissue. Do not rub the injection site. If needed, you may cover the injection site with a plaster.
8. Only use each pre-filled syringe for one injection. DO NOT use any DENSUCOR that is left in the syringe.

Remember: if you have any problems, please ask your doctor or healthcare provider for help and advice.
Disposing of used syringes
- **DO NOT** put the cover back on used needles.
- Keep used syringes out of the reach and sight of children.
- The used syringe should be disposed of in accordance with local requirements. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

3001318-V00

PRODUCT NAME :	DENSUCOR _Inj.	**COUNTRY :** Domestic P2P	**LOCATION :** Enzene Bio.	**SUPERSEDES A/W NO. :**			
ITEM / PACK :	Insert	**NO. OF COLORS : 4**	**SUBSTRATE :**				
DESIGN STYLE :	Front / Back	**PANTONE SHADE Nos. :**	**REMARK :**				
CODE :	8101996-9093	**CMYK**	**Activities**	**Department**	**Name**	**Signature**	**Date**
DIMENSION (MM) :	140 x 500 mm		**Prepared By**	**Pkg.Dev**			
ART WORK SIZE :	S/S		**Reviewed By**	**Pkg.Dev**			
DATE :	20-08-2025		**Reviewed By**	**CR**			
			Approved By	**Quality**			
			Approved By	**Quality**			

This colour proof is not colour binding. Follow pantone shade reference for actual colour matching.