Conexxence®
denosumab-bnht

FDA-approved biosimilar to Prolia® (denosumab)[1]

Step forward with more confidence

Empower patients with a stronger foundation in bone health

INDICATIONS:

CONEXXENCE® (denosumab-bnht) is indicated for:

- Postmenopausal women with osteoporosis at high risk for fracture
- Men with osteoporosis at high risk for fracture
- Men and women with glucocorticoid-induced osteoporosis at high risk for fracture
- Increasing bone mass in men at at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer
- Increasing bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

IMPORTANT SAFETY INFORMATION

SEVERE HYPOCALCEMIA IN PATIENTS WITH ADVANCED KIDNEY DISEASE:

Patients with advanced chronic kidney disease are at greater risk of severe hypocalcemia following denosumab products administration. Severe hypocalcemia resulting in hospitalization, life-threatening events and fatal cases have been reported. The presence of chronic kidney disease-mineral bone disorder (CKD-MBD) markedly increases the risk of hypocalcemia. Prior to initiating Conexxence in patients with advanced chronic kidney disease, evaluate for the presence of CKD-MBD. Treatment with Conexxence in these patients should be supervised by a healthcare provider with expertise in the diagnosis and management of CKD-MBD.

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FDA APPROVED

Clinical development ensured that CONEXXENCE® (denosumab-bnht) met FDA requirements for biosimilarity[1-5]

FDA Requirements for Biosimilar Approval	CONEXXENCE®
Analytical characterization (primary structure, potency, and purity)	✓
Nonclinical studies	✓
Clinical pharmacology	✓
Comparative clinical study	✓
CONEXXENCE® was studied in a Phase III study with a switching arm[4]	

FDA approved based on proven similarity to Prolia® (denosumab) in[1-5]:

- Analytical characterization
- Pharmacokinetics/pharmacodynamics
- Efficacy, safety, and immunogenicity

Demonstrated efficacy at year 1 with similar efficacy in patients who switched to CONEXXENCE®[4]

FDA = US Food and Drug Administration.

Important Safety Information (continued)

CONTRAINDICATIONS

Patients with hypocalcemia

Pre-existing hypocalcemia must be corrected prior to initiating therapy with Conexxence.

Pregnant women

Denosumab products may cause fetal harm when administered to a pregnant woman. In women of reproductive potential, pregnancy testing should be performed prior to initiating treatment with Conexxence.

Patients with hypersensitivity to denosumab products

Conexxence is contraindicated in patients with a history of systemic hypersensitivity to any component of the product. Reactions have included anaphylaxis, facial swelling, and urticaria.

WARNINGS AND PRECAUTIONS

Severe Hypocalcemia and Mineral Metabolism Changes

Denosumab products can cause severe hypocalcemia and fatal cases have been reported. Preexisting hypocalcemia must be corrected prior to initiating therapy with Conexxence. Adequately supplement all patients with calcium and vitamin D.

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PRODUCT FEATURES AND DOSING

Key administration features with CONEXXENCE® (denosumab-bnht)[1-3]

The prefilled syringe enables switching to CONEXXENCE® from Prolia® (denosumab)

Feature	CONEXXENCE®	Prolia®
Safety Needle Guard	Automatic Nemera Safe'n'Sound®	Manual BD Ultra-Safe™
Gauge	29-gauge needle	27-gauge needle
Needle Cover	Latex free	Latex free
Pack Size	1	1
Room Temperature Storage	14 days at 77°F (25°C)	30 days at 77°F (25°C)
Shelf life	30 months	48 months

Equipped with a 29-gauge needle that may enhance patient comfort and an automatic needle safety guard for improved needlestick prevention[6,7]

Dosing[1]

Administer one CONEXXENCE® 60 mg injection every 6 months:

- The recommended dose of CONEXXENCE® is 60 mg administered as a single subcutaneous injection once every 6 months.
- Administer CONEXXENCE® via subcutaneous injection in the upper arm, the upper thigh, or the abdomen.
- Instruct patients to take 1000 mg calcium and at least 400 IU vitamin D every day.

Prefilled Syringe

Important Safety Information (continued)

In patients without advanced chronic kidney disease who are predisposed to hypocalcemia and disturbances of mineral metabolism, assess serum calcium and mineral levels (phosphorus and magnesium) 10 to 14 days after Conexxence injection. In some postmarketing cases, hypocalcemia persisted for weeks or months and required frequent monitoring and intravenous and/or oral calcium replacement, with or without vitamin D.

Patients with Advanced Chronic Kidney Disease

Patients with advanced chronic kidney disease [i.e., eGFR < 30 mL/min/1.73 m^2] including dialysis-dependent patients are at greater risk for severe hypocalcemia

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FRESENIUS KABI BIOSIMILARS

At Fresenius Kabi, our global expertise in complex medicine, state-of-the-art supply chain, and manufacturing allow us to deliver consistent quality biosimilars.

A strong history of scientific expertise, quality manufacturing, and reliable supply

A robust portfolio of **FDA-approved biosimilars in oncology, immunology, and bone health**

Multiple additional biosimilars in development

Winner of Numerous Awards[2]

Important Safety Information (continued)

following denosumab products administration. Severe hypocalcemia resulting in hospitalization, life-threatening events and fatal cases have been reported. The presence of underlying chronic kidney disease-mineral bone disorder (CKD-MBD, renal osteodystrophy) markedly increases the risk of hypocalcemia. Concomitant use of calcimimetic drugs may also worsen hypocalcemia risk.

To minimize the risk of hypocalcemia in patients with advanced chronic kidney disease, evaluate for the presence of chronic kidney disease mineral and bone disorder with intact parathyroid hormone (iPTH), serum calcium, 25(OH) vitamin D, and $1,25(OH)_2$ vitamin D prior to decisions regarding Conexxence treatment. Consider also assessing bone turnover status (serum markers of bone turnover or bone biopsy) to evaluate the underlying bone disease that may be present. Monitor serum calcium weekly for the first month after Conexxence administration and monthly thereafter. Instruct all patients with advanced chronic kidney disease, including those who are dialysis-dependent, about the symptoms of hypocalcemia and the importance of maintaining serum calcium levels with adequate calcium and activated vitamin D supplementation. Treatment with Conexxence in these patients should be supervised by a healthcare provider who is experienced in diagnosis and management of CKD-MBD.

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Important Safety Information (continued)

Drug Products with Same Active Ingredient

Patients receiving Conexxence should not receive other denosumab products concomitantly.

Hypersensitivity

Clinically significant hypersensitivity including anaphylaxis has been reported with denosumab products. Symptoms have included hypotension, dyspnea, throat tightness, facial and upper airway edema, pruritus, and urticaria. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue further use of Conexxence.

Osteonecrosis of the Jaw (ONJ)

ONJ, which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing. ONJ has been reported in patients receiving denosumab products. An oral exam should be performed by the prescriber prior to initiation of Conexxence. A dental examination with appropriate preventive dentistry is recommended prior to treatment with Conexxence in patients with risk factors for ONJ such as invasive dental procedures, diagnosis of cancer, concomitant therapies (e.g. chemotherapy, corticosteroids, angiogenesis inhibitors), poor oral hygiene, and comorbid disorders. Good oral hygiene practices should be maintained during treatment with Conexxence. Concomitant administration of drugs associated with ONJ may increase the risk of developing ONJ. The risk of ONJ may increase with duration of exposure to denosumab products.

For patients requiring invasive dental procedures, clinical judgment should guide the management plan of each patient. Patients who are suspected of having or who develop ONJ while on Conexxence should receive care by a dentist or an oral surgeon. Extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of Conexxence therapy should be considered based on individual benefit-risk assessment.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical low energy or low trauma fractures of the shaft have been reported in patients receiving denosumab products. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with antiresorptive agents. During Conexxence treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Any patient who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Interruption of Conexxence therapy should be considered, pending a benefit-risk assessment, on an individual basis.

Multiple Vertebral Fractures (MVF) Following Discontinuation of Treatment

Following discontinuation of denosumab treatment, fracture risk increases, including the risk of multiple vertebral fractures. New vertebral fractures occurred as early as 7 months (on average 19 months) after the last dose of denosumab. Prior vertebral fracture was a predictor of multiple vertebral fractures after denosumab discontinuation. Evaluate an individual's benefit-risk before initiating treatment with Conexxence. If Conexxence treatment is discontinued, patients should be transitioned to an alternative antiresorptive therapy.

Serious Infections

In a clinical trial of over 7800 women with postmenopausal osteoporosis, serious infections leading to hospitalization were reported more frequently in the denosumab group than in the placebo group. Serious skin infections, as well as infections of the abdomen, urinary tract, and ear, were more frequent in patients treated with denosumab.

Endocarditis was also reported more frequently in denosumab-treated patients. The incidence of opportunistic infections was similar between placebo and denosumab groups, and the overall incidence of infections was similar between the treatment groups. Advise patients to seek prompt medical attention if they develop signs or symptoms of severe infection, including cellulitis.

Patients on concomitant immunosuppressant agents or with impaired immune systems may be at increased risk for serious infections. In patients who develop serious

infections while on Conexxence, prescribers should assess the need for continued Conexxence therapy.

Dermatologic Adverse Reactions

In a clinical trial of over 7800 women with postmenopausal osteoporosis, epidermal and dermal adverse events such as dermatitis, eczema, and rashes occurred at a significantly higher rate in the denosumab group compared to the placebo group. Most of these events were not specific to the injection site. Consider discontinuing Conexxence if severe symptoms develop.

Musculoskeletal Pain

Severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking denosumab products. Consider discontinuing use if severe symptoms develop.

Suppression of Bone Turnover

Treatment with denosumab resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. The significance of these findings and the effect of long-term treatment with denosumab products are unknown. Monitor patients for consequences, including ONJ, atypical fractures, and delayed fracture healing.

Hypercalcemia in Pediatric Patients with Osteogenesis Imperfecta

Conexxence is not approved for use in pediatric patients. Hypercalcemia has been reported in pediatric patients with osteogenesis imperfecta treated with denosumab products. Some cases required hospitalization.

ADVERSE REACTIONS

The most common adverse reactions reported with denosumab products in patients with postmenopausal osteoporosis are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis. The most common adverse reactions leading to discontinuation of denosumab products in patients with postmenopausal osteoporosis are back pain and constipation. The most common adverse reactions reported with denosumab products in men with osteoporosis are back pain, arthralgia, and nasopharyngitis. Pancreatitis has been reported with denosumab. The overall incidence of new malignancies in postmenopausal women with osteoporosis was 4.3% in the placebo and 4.8% in the denosumab groups, and in men with osteoporosis, no patients in the placebo group and 3.3% in the denosumab group. A causal relationship to drug exposure has not been established.

The most common adverse reactions reported with denosumab products in patients with glucocorticoid-induced osteoporosis are back pain, hypertension, bronchitis, and headache.

The most common adverse reactions reported with denosumab products in patients with bone loss receiving ADT for prostate cancer or adjuvant AI therapy for breast cancer are arthralgia and back pain. Pain in extremity and musculoskeletal pain have also been reported in clinical trials. Additionally, in denosumab-treated men with nonmetastatic prostate cancer receiving ADT, a greater incidence of cataracts was observed

INDICATIONS

Conexxence (denosumab-bnht) is indicated for treatment:

- of postmenopausal women with osteoporosis at high risk for fracture
- to increase bone mass in men with osteoporosis at high risk for fracture
- of glucocorticoid-induced osteoporosis in men and women at high risk for fracture
- to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer
- to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

NOTES

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CONEXXENCE® (denosumab-bnht): Step forward with more confidence

No clinically meaningful differences to Prolia® (denosumab)[1-5]

Safe and effective switching from Prolia®[4]

A potentially cost-effective option that may increase access to denosumab

The prefilled syringe features a 29-gauge thin-wall needle and automatic needle safety guard[1,2]

Only one 60 mg CONEXXENCE® injection every 6 months[1]

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References: 1. CONEXXENCE®. Package insert. Fresenius Kabi USA, LLC; 2025. **2.** Data on file. Fresenius Kabi. **3.** Prolia®. Package insert. Amgen Inc; 2024. **4.** Sadek J, Valter I, de Souza A, Szeles P, Monnet J. A randomized, double-blind, study to evaluate the efficacy, pharmacodynamics, safety and immunogenicity of FKS518 proposed biosimilar to denosumab with the originator in postmenopausal women with osteoporosis (LUMIADE-3 study). *Journal of Clinical Oncology.* 2024;42(16_suppl):3155-3155. doi:10.1200/jco.2024.42.16_suppl.3155. **5.** Sadek J, Dryja A, Szeles P, Buccarello AL, Monnet J. A double-blind, randomized, two-arm, single-dose, parallel-group study in healthy participants to compare the pharmacokinetics, pharmacodynamics, and immunogenicity of FKS518 proposed biosimilar to denosumab with the originator (LUMIADE-1 study). *Journal of Clinical Oncology*. 2024;42(16_suppl). doi:10.1200/jco.2024.42.16_suppl.e15097. **6.** Arendt-Nielsen L, Egekvist H, Bjerring P. Pain following controlled cutaneous insertion of needles with different diameters. *Somatosens Mot Res*. 2006;23(1-2):37-43. doi:10.1080/08990220600700925 **7.** Tosini W, Pires J, Dufresne P, et al. Needlestick injury rates according to different types of safety-engineered devices: results of a French multicenter study. *Infect Control Hosp Epidemiol*. 2010;31(4): 401-407. doi: 10.1086/651301

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