# Therapeutic Reviews



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## Denosumab AHFS 92:24

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**Class:** Monoclonal antibody.

**Indications:** Authorized indications vary between products and among countries; consult PI for details. Prevention of skeletal-related events (SRE) in patients with bone metastases from solid tumors and in multiple myeloma; refractory tumor-induced hypercalcemia;[1] giant cell tumor of bone; treatment of bone loss in patients at high risk of fracture receiving hormone deprivation therapy for early prostate or breast cancer, or long-term systemic glucocorticoid therapy; osteoporosis in postmenopausal women and men.

**Contra-indications:** Hypocalcemia, unhealed lesions from dental or oral surgery (also see Undesirable effects).[2,3]

### Pharmacology

Denosumab is a human monoclonal antibody that binds Receptor Activator of Nuclear factor Kappa β Ligand (RANKL), a cytokine and member of the tumor necrosis factor superfamily. This prevents interaction between RANKL and the RANK receptor on osteoclasts, inhibiting their maturation, function and survival. Consequentially, bone resorption is inhibited. Bisphosphonates also inhibit osteoclast function (via a different mechanism) and thereby have similar effects. Although denosumab and bisphosphonates share indications and undesirable effects, the latter drugs are significantly less expensive.

Denosumab is administered by SC injection. Pharmacokinetics in adults are unaffected by changes in age or renal function, although the risk of hypocalcemia is increased in renal impairment (see Undesirable effects). Pharmacokinetics in hepatic impairment have not been studied but are not expected to be altered.

Denosumab is used in a range of clinical settings. It may be the preferred alternative to a bisphosphonate in some settings, e.g. severe renal impairment, or when a bisphosphonate is ineffective. The following highlights its use in populations with serious illness:

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***Prevention of skeletal-related events (SRE) in adults with advanced malignancies involving bone***

SRE include pathological fracture, spinal cord compression, pain and need for radiation or surgery to bone. Those used as outcomes vary between studies, as does their definition, e.g. radiological vs. clinical pathological fracture; this variation can limit direct comparison of study findings.

***Bone metastases from solid tumors***

Denosumab is superior to zoledronic acid in reducing the risk and rate of SRE in patients with bone metastases from solid tumors, particularly breast cancer.[4] Further, denosumab is more effective in delaying the development of painful SRE and the onset of moderate−severe pain in these patients.[5] However, because any analgesic effect of denosumab is modest, patients with *existing* bone pain should be managed with usual analgesic approaches.[6,7]

In contrast to zoledronic acid, which is considered cost-effective in the prevention of SRE associated with advanced cancer, denosumab yields modest health gains at substantial additional cost.[8] Nonetheless, specialty guidelines generally recommend the preventative use of either zoledronic acid or denosumab for all patients with bone metastases arising from breast or hormone-refractory prostate cancer, and for selected patients with other solid tumors, i.e. those considered at high risk of a SRE with a likely prognosis >3 months.[7,9] Apart from cost, other factors influencing choice between zoledronic acid and denosumab include route of administration (IV vs. SC) and the risks of renal toxicity, an acute phase response (both lower with denosumab), and hypocalcemia (lower with zoledronic acid).

The preventative effects on SRE of zoledronic acid and denosumab do *not* overall translate into improved survival.[10] However, a *post hoc* analysis of data from one study of patients with NSCLC found that, compared with zoledronic acid, denosumab was associated with a better median survival (9.5 vs. 8 months; HR 0.8 [0.7−0.9], p=0.01).[11] Although this finding is not definitive (results from a large RCT are awaited), it is suggested that it may relate to the potentially disruptive effects of denosumab on the tumor−bone microenvironment ± a direct inhibitory effect on RANK-expressing cancer cells.[11]

*Multiple myeloma*

In multiple myeloma, denosumab is non-inferior to zoledronic acid in delaying the time to first SRE, but is associated with a lower incidence of renal toxicity (12% vs. 17%).[12] Although specialty guidelines note that denosumab is an option, particularly in those with renal impairment, generally they favour an IV bisphosphonate, based on their lower cost and more flexible dosing interval, e.g. zoledronic acid can be reduced to every 3 months in those without active myeloma on maintenance treatment.[13]

A *post hoc* analysis of a multiple myeloma subgroup had initially raised concerns that denosumab, compared with zoledronic acid, was associated with a worse overall survival.[14] However, no difference was subsequently found in a large RCT and denosumab is now authorized for use in multiple myeloma.[12]

***Treatment of bone loss in patients at high risk of fracture receiving hormone deprivation therapy for early prostate or breast cancer, or long-term systemic glucocorticoid therapy***

Androgen and estrogen deprivation therapy accelerates bone turnover leading to a reduction in bone mineral density (BMD) and a 40−50% increase in fracture incidence. Thus, specialty guidelines generally suggest that in early stage prostate or breast cancer, men treated with androgen deprivation therapy or women treated with an aromatase inhibitor or ovarian suppression (including premenopausal women rendered prematurely postmenopausal, e.g. by chemotherapy) should have their bone health monitored every 1−2 years for fracture risk.[9]

An overall fracture risk is determined based on BMD and the presence of additional risk factors, e.g. age >65 years, current or past smoker, personal or family history of fragility fracture, long-term glucocorticoid use. Correctable risk factors should be addressed, and all advised to consume a calcium enriched diet, to exercise moderately and take vitamin D supplements, with bisphosphonate or denosumab therapy reserved for those at greatest risk. These recommendations, including monitoring bone health, can also be applied to patients receiving long-term systemic glucocorticoid therapy.

In prostate cancer, denosumab 60mg every 6 months reduced the incidence of vertebral fracture from 4% to 1.5% in a 3 year RCT.[15] However, zoledronic acid 4mg every 6−12 months is an accepted alternative.[9] In breast cancer, the use of a bisphosphonate PO/IV or denosumab 60mg appears sufficient to prevent treatment-related bone loss.[9]

***Tumor-induced hypercalcemia***
Denosumab is of benefit in hypercalcemia (albumin-corrected plasma calcium >12mg/dL) that has failed to respond to bisphosphonate therapy. Initial dosing is at 1−2 week intervals (see Dose and use). In a large case series, calcium levels were ≤11.6mg/dL in two thirds of patients, by day 10, with normocalcemia achieved in one third. Overall, a partial or complete response was seen in 70% and 64% of patients respectively, with a median duration of response of 15 weeks.[1] Such use is authorized in the USA.

***Giant cell tumor of bone***
Denosumab is used to impede the growth of giant cell tumors of the bone in skeletally mature adolescents and adults, improving local control and/or facilitating less invasive surgical treatments.[16]

***Bio-availability*** 60−80% SC (partly due to pre-systemic catabolism).
***Onset of action*** 3 days (80% reduction in bone resorption markers ≤1 week).
***Time to peak plasma concentration*** 10 days.
***Plasma halflife*** 28 days.
***Duration of action*** weeks−months.

**Cautions**
Renal impairment or ESKD (increased risk of hypocalcemia). Patients with risk factors for osteonecrosis of the jaw or of the external auditory canal (see Undesirable effects).

**Drug interactions**
Clinically significant pharmacokinetic interactions have not been reported and are unlikely.

**Undesirable effects**
***Very common (>10%):*** breathlessness, diarrhea, hypocalcemia (see below), musculoskeletal pain.
***Common (<10%, >1%):*** hypophosphatemia, hyperhidrosis, osteonecrosis of jaw (see below), tooth extraction, rash. New primary cancers (see below).
***Rare (<0.1%, >0.01%):*** atypical femoral fracture.
***Not known***: osteonecrosis of external auditory canal.

***Hypocalcemia***
In patients with bone metastases from solid tumors, hypocalcemia is twice as common with denosumab 120mg (10%) than zoledronic acid (5%).[17] In multiple myeloma, the incidence is 17% vs. 12%, respectively.[12] It mostly occurs ≤2 weeks of starting treatment and can be severe and life-threating.[18] Those with renal impairment or ESKD are at increased risk.

Severe hypocalcemia is rare with denosumab 60mg, and generally occurs in those with additional risk factors for hypocalcemia, e.g. electrolyte imbalance, severe renal impairment/dialysis.[17,19]

Pre-existing hypocalcemia must be corrected before starting denosumab. Except when used for tumor-induced hypercalcemia, daily oral supplementation with calcium and vitamin D is recommended. Calcium levels should be monitored regularly, particularly in those at increased risk, e.g. severe renal impairment/dialysis (see Dose and use).[18]

***Osteonecrosis of the jaw and external auditory canal***
The incidence of osteonecrosis of the jaw (ONJ) with denosumab 120mg is similar to that with zoledronic acid in patients with bone metastases from solid tumors (~1.5%) and multiple myeloma (~4%).[12,17] Duration of exposure, history of tooth extraction, poor oral hygiene, use of a dental appliance and concurrent or previous chemotherapy affect the risk of ONJ. The risk of this complication continues for ≤5 months after stopping treatment. Patients should be counselled and issued with cards to remind them of the precautions to follow before and during treatment, including the need for dental check-ups. Unhealed lesions from dental or other oral surgery is a contra-indication to the use of denosumab 120mg.[2,3]

As with bisphosphonates, osteonecrosis of the external auditory canal can also occur. The incidence is unknown. Possible risk factors include corticosteroid use, chemotherapy ± local infection or trauma. Patients should be counselled to report ear pain, discharge, or infection during treatment.[20]

The risk of ONJ and osteonecrosis of the external auditory canal is related to cumulative dose and is thus less with denosumab 60mg.

***Other toxicities***

*Atypical femoral fractures:* Denosumab (like bisphosphonates) is associated with rare cases of atypical femoral fracture affecting the subtrochanteric and diaphyseal regions, often bilaterally and occurring with minimal or no trauma. Patients should be advised to report new or unusual thigh, hip or groin pain.[21] If a fracture occurs, denosumab should be discontinued and an orthopedic opinion obtained.

*Discontinuation fractures:* Unlike bisphosphonates, denosumab is not taken up into bone. In osteoporosis, after discontinuation of denosumab, bone turnover increases within 3 months, bone mineral density falls to baseline levels within 12 months and there is an increased risk of multiple vertebral fractures.[22] Thus, when used for osteoporosis, denosumab should be administered regularly, and if discontinued, a bisphosphonate used instead. By extrapolation, the same considerations apply to its use in the cancer setting and denosumab is generally given indefinitely, until the patient is in the last weeks of life.

*Infection:* RANK receptors are also expressed on immune cells, e.g. lymphocytes, macrophages. Although denosumab potentially could impede immune activation, a meta-analysis of RCTs in osteoporosis suggests no significantly increased risk of severe infection.[23] Nonetheless, in one large RCT, more participants receiving denosumab than placebo experienced severe skin infections, mostly erysipelas/cellulitis of the lower limb, although numbers affected were small (15 vs. 3).[24] It is suggested that inhibition of RANKL in keratinocytes could reduce the number of regulatory T cells, increasing the inflammatory response to a skin infection and thereby resulting in a more severe appearance.[25] Studies in other settings, including advanced cancer, have found no increased risk of infection.[25]

*New primary cancers:* In a pooled analysis of four studies of patients with advanced cancer receiving treatment to reduce SRE (median duration ~1 year), the incidence of a new primary cancer was twice as common with denosumab 120mg (1.1%) vs. zoledronic acid 4mg (0.6%); the full implications of this recent observation are currently uncertain (Amgen, Direct Healthcare Professional Communication, 2018).

**Dose and use**

Generally, either denosumab or a bisphosphonate is used, but not both concurrently.

Pre-existing hypocalcemia must be corrected before starting denosumab. During treatment with denosumab (unless given for hypercalcemia) daily oral supplements of elemental calcium ≥500mg and vitamin D 400 units should be given, e.g. Caltrate® 600+D.

Denosumab is administered as a SC injection into the thigh, abdomen or upper arm. To reduce discomfort at the site of injection, allow the vial to reach room temperature before use (also see Supply).

***Baseline assessment and monitoring***

All plasma calcium values are albumin-corrected.

Unless hypercalcemia is present, plasma calcium should be within the normal range before the initial dose of denosumab is given. Thereafter, it should be monitored, at minimum:[18]

**Box A. Emergency treatment of hypocalcemia**[26]

*EKG monitoring is required because of the risk of cardiac arrhythmias.*

*Note: For patients with raised plasma phosphate levels, consult specialist renal and/or endocrinology guidance.*

**Initial treatment**

- give 10−20mL calcium gluconate 10% (2.2−4.4mmol) IV diluted in 50−100mL sodium chloride 0.9% or glucose 5% over 10min
- use a central or large peripheral vein because of the risk of irritation
- repeat the dose until the patient is asymptomatic.

**Follow up infusion**

- give 100mL calcium gluconate 10% (22mmol) IVI diluted in 1L sodium chloride 0.9% or glucose 5% at a rate of 50−100mL/h; titrate to achieve normocalcemia
- check calcium levels 2h after the infusion.

- within two weeks of an initial 120mg dose; consider ongoing monitoring, e.g. prior to each dose, in patients with risk factors for hypocalcemia, e.g. severe renal impairment/dialysis
- within two weeks of an initial 60mg dose in patients with risk factors for hypocalcemia
- before each 6 monthly 60mg dose
- if symptoms of hypocalcemia occur; counsel patients to report muscle spasms, twitches, cramps, numbness or tingling in the fingers, toes, or around the mouth.

If hypocalcemia occurs, when mild (plasma calcium ≥7.6−8.8mg/dL and asymptomatic) an increase in PO calcium supplementation to 2−4g/24h may suffice. However, severe (plasma calcium <7.6mg/dL) or symptomatic hypocalcemia is a *medical emergency* and requires IV calcium gluconate (Box A).[26]

The following precautions should be taken to reduce the risk of ONJ (also see Undesirable effects):[18]

- denosumab 120mg; a dental examination and appropriate preventative dentistry is recommended before treatment. Denosumab should not be started if patients require dental or jaw surgery, or if they have not recovered from oral surgery
- denosumab 60mg; check for ONJ risk factors before treatment and if present, a dental examination and appropriate preventative dentistry is recommended.

Patients should be counselled on the risks and to report symptoms associated with hypocalcemia, ONJ, osteonecrosis of the ear, and atypical fracture.

**Box B. Prevention of SRE in patients with a limited prognosis**

*PCF* notes that:

- the cost-effectiveness of the additional benefit of denosumab over zoledronic acid for the prevention of SRE is questionable
- the risk of discontinuation fractures is greater with denosumab than zoledronic acid
- speciality guidelines generally recommend the use of either.

Thus, for patients with cancer referred to a specialist palliative care service who have progressive metastatic bone disease despite monthly denosumab, unless there is severe renal impairment, *PCF* recommends considering substituting the denosumab for zoledronic acid. For patients with a limited prognosis, the zoledronic acid would need to be given only once, 4 weeks after the last dose of denosumab. However, if necessary, the zoledronic acid can be repeated every 3 months.

***Prevention of skeletal-related events (SRE) in adults with advanced malignancies involving bone***

For all patients with breast or hormone-refractory prostate cancer with bone metastases, whether symptomatic or not. For selected patients with other solid tumors (i.e. those considered at high risk of a SRE with a likely prognosis >3 months) or multiple myeloma:

- give 120mg SC every 4 weeks
- continue indefinitely, until patient is in last weeks of life (also see Box B).

Ongoing trials are comparing dosing intervals of 4 vs. 12 weeks in breast and prostate cancer.[7] In multiple myeloma, IV bisphosphonates are generally preferred.[13]

***Treatment of bone loss in patients at high risk of fracture receiving hormone deprivation therapy for early prostate or breast cancer, or long-term systemic glucocorticoid therapy***

In addition to general measures (see Pharmacology):

- give 60mg SC every 6 months.

Bisphosphonates are suitable alternatives.

***Tumor-induced hypercalcemia***

Generally, used for hypercalcemia refractory to bisphosphonate therapy (see Pharmacology):

- give 120mg SC every 4 weeks; *give additional 120mg SC doses on days 8 and 15 of the first month of therapy*
- monitor at regular intervals for ongoing benefit.

***Giant cell tumor of bone***

Authorized as an alternative to surgery. Dose schedule as per tumor-induced hypercalcemia above.

## *Abbreviations/key*

| | |
|---|---|
| † | Off-label use |
| EKG | Electrocardiogram |
| ESKD | End-stage kidney disease |
| HR | Hazard ratio |
| min | Minute(s) |
| ONJ | Osteonecrosis of the jaw |
| PCF | Palliative Care Formulary |
| PI | Package insert (USA), equivalent to SPC (UK) |
| PO | Per os, by mouth |
| IV | Intravenous |
| IVI | Intravenous infusion |
| NSCLC | Non-small cell lung cancer |
| RCT | Randomized controlled trial |
| SC | Subcutaneous |
| SRE | Skeletal-related event |

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