



CADTH

Common Drug Review *Patient Group Input Submissions*

Denosumab (Prolia) for osteoporosis, postmenopausal women

Patient group input submissions were received from the following patient groups. Those with permission to post are included in this document.

Osteoporosis Canada — permission granted to post

Arthritis Consumer Experts - permission granted to post

CADTH received patient group input for this review on or before December 14, 2015

CADTH posts all patient input submissions to the Common Drug Review received on or after February 1, 2014 for which permission has been given by the submitter. This includes patient input received from individual patients and caregivers as part of that pilot project.

The views expressed in each submission are those of the submitting organization or individual; not necessarily the views of CADTH or of other organizations. While CADTH formats the patient input submissions for posting, it does not edit the content of the submissions.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no personal information is included in the submission. The name of the submitting patient group and all conflict of interest information are included in the posted patient group submission; however, the name of the author, including the name of an individual patient or caregiver submitting the patient input, are not posted.

Osteoporosis Canada

Osteoporosis Canada responses to questions posed by CADTH regarding denosumab - Prolia

All of these answers are based on the evidence that was used to create the 2010 clinical practice guidelines. These guidelines and the Quick Reference Guide may be accessed at
<http://www.osteoporosis.ca/health-care-professionals/clinical-tools-and-resources/>

1. How should fracture risk be best described?

It is best determined using a fracture assessment tool such as CAROC or FRAX that combines clinical risk factors and the result of bone mineral density measured at the hip. If the probability of sustaining a fragility fracture at major osteoporotic sites (hip, vertebrae, humerus and distal forearm) is moderate (10 to 20%) or high (over 20%) over the next year, pharmacological therapy may be considered.

For example, taking a 65 year old woman, the categories are as follows:

- **Low risk:** hip T-score -1.9 or better; no fragility fracture after age 40; no other risk factors that would bump them into next category
- **Moderate risk:** hip T-score -1.9 to -3.5; if T-score better than -1.9, then having one or more risk factors that bump the individual from low to moderate
- **High risk:** hip T-score -3.5 or worse; or risk factors that bump the individual from low or moderate to high. There are circumstances that put an individual in the high risk category regardless of T-score:
 - having had a fragility fracture after age 40 **and** being on steroids; or having had a spine fracture; or having had a hip fracture; or having had two or more fragility fractures (excluding fractures of the skull, hands, ankles or feet).

2. Is there a place for age (>75 years) or bone density scores, or are these adequately captured within fracture risk?

We feel that the use of the fracture assessment tools reliably captures patients who are at high risk of fragility fractures and that age and BMD alone might not reflect accurately the risk of fractures. For example, a patient who has sustained a fragility humerus fracture may have a BMD that is not below-2.5 nor older than 75 years, yet their risk for future fracture may be higher than 20% and would therefore benefit from antiresorptive therapy such as denosumab.

3. How should bisphosphonate failure be best described?

There is no definite definition of treatment failure. Most would agree that patients who continue to fracture, while on therapy (and compliant with therapy) for a period of 12 months could be considered as having failed therapy. Other failures of therapy include significant bone mineral density loss despite therapy or persistently elevated bone turnover markers while receiving antiresorptive therapy.

4. How should bisphosphonate intolerance be best described?

The most common side effect of oral bisphosphonates is heartburn and irritation of the esophagus. Nausea, abdominal pain and loose bowel movements may occur. Bone, joint and/or muscle pain has been reported infrequently by patients taking bisphosphonates. If the patient takes the medication correctly, adhering to the instructions on how to take a bisphosphonate, and still experiences one or more of these side effects to the extent that they cannot tolerate the medication, this is bisphosphonate intolerance. Bisphosphonates should not be administered to patients who have impaired kidney function (creatinine clearance lower than 30 ml per min) and denosumab should be considered as the optimal choice for treatment in this population.

Arthritis Consumer Experts

Arthritis Consumer Experts received three different inputs for our call for patient input on CADTH's request for advice for denosumab for osteoporosis, postmenopausal women – one from a patient living with rheumatoid arthritis and osteoarthritis, one from a Professor [REDACTED], and one from a rheumatologist. Below is a summary of what each person's feedback on the four questions proposed by CADTH.

1. How should fracture risk be best described?

According to the patient, "fracture risk has to be described in terms of individual risk. We can't have a one size fits all, 5 question risk assessment. The fracture risk score seems like a snapshot that lacks enough detail."

In response to this question, the Professor said: "I would suggest that they adopt Osteoporosis Canada's recommendations. They include FRAX scores or CAROC scores that place them in the high risk category. An easier definition may simply be a T-score of less than -2.5 for those over the age of 65 years or those that have had either a hip or spine fracture. The latter would make it easier for more individuals and may also include those who are only at moderate risk for fracture."

The rheumatologist we interviewed believes that further research is needed to determine measurements of fracture risk. He does recommend an article titled "Fragility fracture: recent developments in risk assessment", published by T.J. Asprey in Therapeutic Advances in Musculoskeletal Disease, where fracture risk is well reviewed. In the meantime, he thinks the best approach is to use risk assessment tools such as the Fracture Risk Assessment Tool (FRAX) and the Canadian Association of Radiologists and Osteoporosis Canada (CAROC) system. He added: "A case can be made for the use of FRAX without DEXA results and this would certainly make this more widely useful, even in Canada. The argument that lack of internet accessibility is someone specious, in my opinion. Internet access is much more widespread than that of the dual energy X-ray absorptiometry (DEXA)."

2. Is there a place for age (>75 years) or bone density scores, or are these adequately captured within fracture risk?

The patient feels that bone density must be considered because it is "so much easier to fracture bone with less solid architecture." In her words: "With inflammatory arthritis increasing the risk by 50%, and family history also as a strong indicator of risk, I think that fracture risk has to be looked at more carefully, with an advanced algorithm for people with any factors that predispose them to be at risk. It concerns me that risk is stratified in terms of bones most commonly fracture. That does not give enough weight to risk in people with a family history of vertebral fractures and no family history of hip fracture. They may be undertreated because of this." She feels that age and bone density has a place being included in fracture risk. Falls risk should also be considered, based on how well people walk without shoes, or the help of orthotics.

Besides adequately capturing fracture risk, the Professor believes age and bone density (BMD) must also be considered. "For the average primary care physician, this is easier to determine than trying to calculate fracture risk," he added.

In response to this question, the rheumatologist said: "Arbitrarily utilizing age, and presumably assigning this greater significance that a cumulative risk fracture score, is illogical. It is one clinical risk factor

among many. DEXA is clearly a strong risk predictor, but as stated in Asprey's article, far from absolute. Clinical risk factors, and particularly a prior fragility fracture, may well 'trump' a DEXA score."

3. How should bisphosphonate failure be best described?

In the patient's point-of-view, failure happens if the bone density of the patient taking bisphosphonates did not improve with the medication.

The Professor recognizes that what is considered as bisphosphonate failure is a subject of much debate. He commented: "As a straw man, I would suggest that those who fracture after year of bisphosphonate therapy be considered treatment failures. I do realize that these drugs are not perfect and fracturing while on treatment is going to happen in some, from a patient perspective fracturing while on treatment is treatment failure. I would also suggest that a decline in BMD either after serial measurements or a single measurement of greater than 30% be considered a treatment failure."

When asked about bisphosphonate failure, the rheumatologist said: "Carioli et al's article in Osteoporosis International (abstract attached) describes an ~25% failure rate of bisphosphonates, likely an underestimate, given the criteria of 2 fragility fractures plus a fall in bone mineral density. My recommendation would be that bisphosphonate failure be defined by the development of a fragility fracture (whether or not symptomatic) following at least 6 months of compliance with the use of an oral bisphosphonate, along with adequate calcium and vitamin D utilization. The use of DEXA as a criterion is compromised by the significant variability of technique and changing of apparatus in many labs. Studies in the past have shown that, in many routine BMD labs, changes over time tend to regress to the mean and are, thus, "meaningless"."

4. How should bisphosphonate intolerance be best described?

According to the patient, bisphosphonate intolerance would be when a patient experiences nausea or other side effects when taking the medication.

The Professor considered intolerance to be any of the following:

- New or increased symptoms of reflux
- New or increased joint pain
- Fever attributed to bisphosphonate use typically seen with IV bisphosphonates or high dose oral bisphosphonates
- Diarrhea attributed to bisphosphonate use

The Professor concluded his feedback by saying that he believes there should be reimbursement for men, using similar criteria to define high risk.

When questioned about bisphosphonate intolerance, the rheumatologist said: "My opinion is that this should be the use of the present CDEC criteria, but supplemented by an OR, "persistent or recurrent gastrointestinal intolerance, despite interventions to control this which will not compromise the absorption of the agent, after at least one month."

The rheumatologist concludes by expressing his opinion on contra-indications to bisphosphonate therapy: "While the listed contra-indications of hypersensitivity and oesophageal abnormalities of stricture or achalasia are reasonable, this fails to take into consideration the patient who simply is intolerant of these agents (i.e., dyspepsia). Even if one were to proceed to the absurd degree of

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subjecting these patients to endoscopic and/or radiologic evaluation of the oesophagus, many persons with dyspepsia sufficient to prevent their use of bisphosphonates would not demonstrate either stricture or achalasia. Accordingly, by this recommendation from CDEC, these patients would be denied funding for denosumab, despite being >75 years, having a prior fragility fracture or having a bone density in the osteoporosis range of $\geq 2.5!$ "