denosumab (PROLIA°) and steroid-induced osteoporosis

NOT ACCEPTABLE

Denosumab has not been shown to prevent clinical fractures, but it has many adverse effects that can be severe or even fatal, including deep infections, hypocalcaemia, osteonecrosis and multiple vertebral fractures after discontinuation.

PROLIA° - _denosumab_ solution for subcutaneous injection

- **60 mg** of *denosumab* per prefilled syringe in 1 ml of solution
- **anti-RANKL monoclonal antibody**
- **New indication**: "*bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture*". [EU centralised procedure]

Prolonged systemic corticosteroid therapy leads to bone loss and an increased risk of fracture. Fracture prevention in patients receiving long-term corticosteroid therapy relies mainly on non-pharmacological measures (fall prevention, regular exercise, adequate dietary intake of calcium and vitamin D), while using the lowest effective dose of the corticosteroid for the shortest possible duration. Bisphosphonates have not been shown to prevent symptomatic fractures in this situation (1,2).

Denosumab (Prolia°, Amgen) is a monoclonal antibody that binds to a cytokine called RANKL that stimulates osteoclast activity and plays a role in immunity. *Denosumab* has an unfavourable harm-benefit balance in the prevention of osteoporotic fractures. It has also been authorised in the prevention of osteoporosis induced by prolonged corticosteroid therapy (3-5).

Denosumab has mainly been evaluated in this situation in a double-blind randomised trial in 795 adults (median age 63 years) who had been taking *prednisone* at a daily dose of at least 7.5 mg, for over 3 months in two-thirds of cases. The patients were randomised to receive either *denosumab* or the bisphosphonate *risedronic acid* for 2 years, in conjunction with *calcium* and *vitamin D* supplementation. After one year of treatment, the increase in bone mineral density (the primary endpoint) was greater in the *denosumab* group than in the *risedronic acid* group ($p<0.001$). This effect persisted after 2 years of treatment (4). However, a similar proportion of patients in the two groups sustained symptomatic fractures (about 5% after one year of treatment) (4).

Denosumab has many adverse effects, which can be severe or even fatal: back, muscle and bone pain; immunosuppressive effects resulting in deep infections including endocarditis and skin infections; hypocalcaemia; osteonecrosis of the jaw or external auditory canal; cataracts; cancer; hypersensitivity reactions; pancreatitis; cardiovascular disorders; autoimmune diseases; alopecia; and multiple vertebral fractures after discontinuation (3,5-7).

No previously unknown adverse effects were reported during the trial discussed above (4). The incidence of serious adverse effects after 2 years of treatment was 24% in both groups (4).

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Literature search up to 12 November 2019

In response to our request for information, Amgen provided us with no documentation on its product.

1- Prescrire Editorial Staff "Corticosteroids: no drug prevention of fractures needed" *Prescrire Int* 2009; **18** (102): 175.
2- Allen CS et al. "Bisphosphonates for steroid-induced osteoporosis" (Cochrane Review) (last update 2016). In: "The Cochrane Library" John Wiley and Sons, Chichester 2016; issue 10: 108 pages.
3- Prescrire Editorial Staff "Denosumab and male osteoporosis. Do not use in men (or in women)" *Prescrire Int* 2016; **25** (168): 36.
4- EMA - CHMP "Public assessment report for Prolia. EMEA/H/C/001120/II/0068" 26 April 2018: 74 pages.
5- Prescrire Rédaction "dénosumab" Interactions Médicamenteuses Prescrire 2020.
6- Prescrire Editorial Staff "Denosumab: immune dysfunction" *Prescrire Int* 2018; **27** (198): 268-269.
7- EMA - PRAC "Minutes of the meeting on 08-11 April 2019" 16 May 2019: 94 pages.