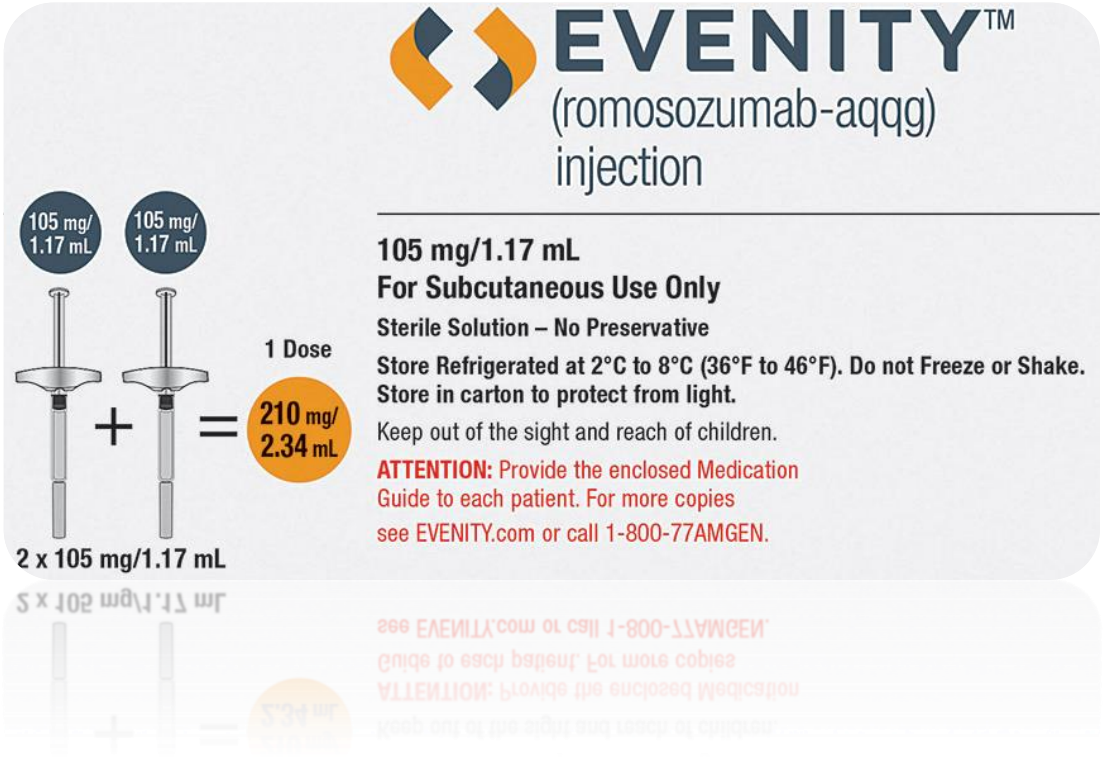
ROMOSOZUMAB, A NEW DRUG TO OSTEOPOROSIS



The FDA approved (April 9th 2019) the first drug for osteoporosis for almost two decades. The drug (a monoclonal antibody) has been developed from the casual observation of a genetic mutation in people with bones of infrequent hardness.

Osteoporosis is a clinical condition characterized by decreased bone mass and deterioration of the microscopic architecture of bone which increases its fragility and, consequently, the risk of fractures.

It is estimated that around 200 million people have fragile bones. One out three women and one out five men will suffer an osteoporotic fracture throughout their lives. For many people, an osteoporotic fracture is the beginning of a disability spiral.

For many years, bisphosphonates have been the main treatment of osteoporosis [(1)]. Bisphosphonates, although slowing bone loss, are not osteogenic drugs.

Inhibitors of the κβ' receptors increase both osteoblastic and osteoclastic activity, although the *net* effect is an increase in bone mass [(2)].

The first monoclonal antibody for the treatment of osteoporosis was denosumab (3).

Denosumab was a monoclonal antibody designed after decipherment by Amgen researchers during the 1990s of the cellular signalling path OPG-RANK-RANKL

OPG is acronym for OsteoProteGerina; RANK is the acronym for Nuclear Activator Receptor κ; and RANKL, is the RANK ligand.

The OPG↔RANK interaction inhibits osteoclastic activity, while the RANK↔RANKL interaction activates osteoclastic activity. Thus, the antibody (denosumab) against RANKL (the RANK ligand) blocks this interaction and, as a result, decreases osteoclastic activity.

The new drug, romosozumab (AMG785 / CDP7851), is marketed under the name of Evenity®. It has been developed as a joint-venture by the American biotechnology company Amgen and the Belgian company UCB.

Romosozumab stimulates osteoblastic activity, without stimulating osteoclastic activity.

The technical information indicates that romosozumab is only recommended to postmenopausal women with high risk of osteoporotic fractures, with the warning of a small but significant increase in the risk of heart attacks or stroke. According to experts, it is an important medicine given that it is the first that seems to directly stimulate the formation of bone tissue.

An increase in bone density of 6% results in a doubling of bone strength. During clinical trials, the group of patients treated with romosozumab showed a statistically significant reduction in the number of fractures, both clinical and subclinical (only radiologically evident).

In a study in which romosozumab was contrasted with alendronate [4] (the standard bisphosphonate), 127 participants in the study group treated with romosozumab (2046 women) suffered fractures, compared with 243 in the control group (2.047), treated with alendronate.

The Achilles heel of romosozumab is a limited and unexpected increase in heart attacks, strokes and sudden deaths: 50 cases in the study group (2040 women treated with romosozumab) *vs* 38 cases of the 2,140 women treated with alendronate. In other words, the percentage incidence of cardiovascular problems was 2.5% (study group) *vs* 1.9% (control group).

However, this difference, with statistical significance, was only reported in one of the two major clinical studies that the FDA routinely requires before authorizing a new drug.

The fundamental clinical study for the authorization of Evenity® has methodological strengths (inclusion of a group of patients with a high risk of fracture), but also weaknesses (lack of a placebo group, as well as not having included in its design a risk assessment cardiovascular).

The approval by the FDA has been conditioned to the requirement to include boxed warning contraindicating the use of romosozumab in patients who have suffered a heart attack or stroke, or be part of groups with high cardiovascular risk. If during the treatment with romosozumab (Evenity®) the patient experiences a vascular accident, the treatment should be stopped immediately.

Adverse effects with romosozumab include arthralgia, headache and irritation at the injection site.

The authorization also entails the requirement to carry out a post-marketing study (phase IV) in order to estimate the cardiovascular risks beyond the limited duration of the clinical trial (1 year).

When the text is written, the Evenity® price has not yet been made public.

The dosage of Evenity® (romosozumab) will be a single monthly injection.

How romosozumab was discovered?

In 1964, a group of Afrikaners affected of sclerostosis was studied in South Africa. They were tall and corpulent, not obese, with unusually large and extraordinarily dense bones. Unfortunately, their bones grew so disproportionately that their heads became deformed. The jaws were deformed as well, and the excessive bone growth of the skull compressed the nerve roots causing mainly deafness (involvement of the VIII cranial nerve) and facial paralysis (involvement of the VII cranial nerve). In addition, they suffered intense headaches; and syndactyly of your index and middle fingers. These people (homozygous) for the mutation have van Buchem's disease. The mutation associated with sclerostosis was discovered in 1955.

People carrying the mutated gene in heterozygous condition (only one of the two mutated alleles) do not suffer from van Buchem's disease, but benefit from bones of exceptional strength. Romosozumab tries to pharmacologically emulate the advantage of people heterozygous for this mutation.

In the year 2001, it was discovered that these effects were due to a single mutation. This unexpected finding led, incidentally, to discover another cellular pathway for the regulation of osteogenesis.

Physiologically there is an elegant and tight turnover between osteoblastic and osteoclastic activities. In the condition of osteopenia and, the most advanced of osteoporosis, this balance is lost in favour of a net loss of bone mass.

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In January 2019, an FDA advisory committee voted to approve Evenity® for 18 *vs*. 1. However, the committee decided to ask Amgen for a more detailed investigation of the potential cardiovascular side effects.

For now, Evenity® will be restricted to postmenopausal women with osteoporosis who have not responded favourably to other treatments.

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