

# Prolia: a pioneer in the world of osteoporosis treatments

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According to Vivian Goldschmidt, MA, “ Prolia was designed to treat and prevent postmenopausal osteoporosis for patients considered to be at high risk of fractures.

” A fairly new kind of drug, Prolia either promises great potential in the world of osteoporosis medications, or it will just add to the world’s wall of shame. Prolia will offers an alternative solution to those who have been failed by Big Pharma’s poor osteoporosis drugs. Theoretically, Prolia sounds as the latest breakthrough in the biopharmaceutical industry, however, all drugs deserve the benefit of the doubt. Due to this, we must ask ourselves what Prolia actually does. Since Prolia is a monoclonal antibody (mAb), on the surface, it seems very complex. However, Prolia’s mechanism and background is quite simple.

Monoclonal antibodies are copies of the same identical antibody, a protein that’s produced to neutralize a certain antigen, such as a virus or fungal pathogen. Receptor activator of nuclear factor-kappaB ligand (RANKL) is a “ protein that activates osteoclasts and is involved in immune-response regulation.” As stated by Amgen, “ the bone is a dynamic tissue that is continually being built, broken down, and rebuilt in a process called bone remodeling. Osteoclasts are multinucleated bone cells that remove old bone by a process called resorption. On the other hand, the cells responsible for building new bone tissue are called osteoblasts.

Osteoclasts make space in order to make room for the new bone material, osteoid, which is constantly being added by osteoblasts, thus replacing old bone. This relationship is the process known as bone remodeling, the way in

which the body can constantly contain strong, healthy bones that are resistant to fractures and breaks. Over time osteoclasts turn into osteocytes. Medical Condition Prolia treats A condition that sometimes results from an imbalance of osteoclasts and osteoblasts is postmenopausal osteoporosis. As defined by the Cleveland Clinic, “ Osteoporosis is a disease that weakens bones, increasing the risk of sudden and unexpected fractures.

” Osteoporosis results in an increased loss of strength and bone density, usually as a result of this imbalance. The disease tends to have no symptoms besides bone pain and aches. In fact, because of this, osteoporosis usually isn’t discovered until a major bone fracture. Once experiencing your first, your doctor will usually test for osteoporosis through a dual X-ray absorptiometry test. This is due to the fact that once experiencing your first bone fracture you are much more susceptible to having another one.

Fractures, such as one to the hips, can hinder daily life and activities. Luckily, treatments, such as Prolia, can also slow the rate of bone loss if you have osteoporosis. Furthermore, it has been linked that the lack of estrogen due to post-menopause usually is associated with the development of osteoporosis. After menopause, bone breakdown outpaces the deposits of osteoid. According to Cleveland Clinic, “ Early menopause and any prolonged periods in which hormone levels are low and menstrual periods are absent or infrequent can cause loss of bone mass.” This is due to the decline in estrogen.

The lack of estrogen only causes RANKL levels to increase leading to hyperactivity of osteoclasts, hence osteoporosis. If gender influences

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osteoporosis, there must be other influences on the likelihood of disease as well. It can be noted that women are four times more likely to develop osteoporosis than men. Because women have lighter, thinner bones they are at a much higher risk. In addition after bone density has reached its peak, usually around the age of 30, bone resorption tends to outpace the creation of new bone. Women around the age of 50 are especially susceptible to osteoporosis.

Furthermore, white and Asian women are more likely to develop osteoporosis, almost about twice as likely as any other minority. As stated before, anyone without a smaller bone structure and body weight, usually will be more likely to develop osteoporosis than someone who has a greater bone density. Genetics is another risk factors for osteoporosis. For example, if any of your elders, within at least 2 generations, have had any signs of osteoporosis, such as a “ fractured hip after a minor fall, you may be at greater risk of developing the disease.” 2 Prolia was approved by the Food and Drug Administration (FDA) to treat postmenopausal osteoporosis.

**Denosumab Description** Denosumab itself is a fully human monoclonal antibody that is produced by Chinese Hamster Ovary cells (CHO).

It consists of 2 heavy and 2 light chains of kappa subclass. Each light chain consists of 215 amino acids (AA) while each heavy chain consists 448 AA. Its molecular weight is 147 kilo Daltons (kDa). Denosumab’s variable region binds to RANKL and inhibits it from binding to RANK. Prolia consists of denosumab, sorbitol, acetate, polysorbate 20, sodium hydroxide and also includes water in its injection form.

Prolia is administered twice a year intravenously in the form of an injection. Mechanism of Action As stated before, denosumab's variable region is able to recognize and bind to RANKL, not allowing RANKL levels to rise. With the inhibition of RANKL, we have the balancing of less osteoclasts associated with osteoclast's failure of function. This reestablishes balance. Acceptance Criteria for a Batch of Prolia Before releasing the batch of Prolia, the shelf life must be pre-determined and validated.

Pharmacopeial tests must also be conducted. As stated by Melbourn Scientific, " pharmacopoeial testing is a requirement for many stages of product manufacture," and it should be tested accordingly to ICH (International Conference for Harmonization) guidelines as well as under good manufacturing practices (GMPs). Universal tests should also be conducted and documented in order to evaluate the description of the dosage, identification, quality of all assay, as well as to detect any impurities. Specific tests must also be conducted and documented to determine dissolution, disintegration, and injection reactivity, uniformity of dosage units, water content, and microbial limits of the batch. Quality Assays All assays for Prolia were designed in accordance with the ICH Q6B guidelines. These assays include: ELISA, peptide mapping, Amino Acid Analysis, DELFIA assay, Dot blot, IEF, and SDS PAGE.

Enzyme linked immune sorbent assay tests are the most commonly run on Prolia throughout the biologic's life cycle. However, in the manufacturing of denosumab, manufacturing and bioanalytical method changes both changed the design of the ELISA protocol. An updated and improved ELISA method

was validated based on previous data from two manufacturing formulation batches. One batch was used as the reference point for the bio comparability of the two assays. However, an ELISA test has been standardized by Amgen for Prolia. The following is a quick overview.

The principle behind an ELISA test is to detect a desired antigen of interest. There are 4 major key steps: coating, blocking, detection and then reading the results. For Prolia's ELISA test to be conducted, an in-house test must be used. To begin the procedure, a polystyrene plate needs to be coated with recombinant human RANKL. Any excess RANKL or other material would then be removed by a wash step. Following this, an assay buffer would then be added to cover the unbound sites.

After completion, biotin-conjugated rabbit anti-denosumab antibody would then be added as a detection reagent. After incubation, streptavidin conjugated to HRP would be added to bind to the complex as well as with some TMB peroxidase substrate solution. The plate would then be incubated and 1 N H<sub>2</sub>SO<sub>4</sub> would be added to stop the color development. According to the NCBI, " the optical density was measured at 450 nm with reference to 650 nm," meaning that in order to interpret the results the optical density would have to be measured to determine the efficiency of the test. An ELISA kit method may also be used, but it is not as common.

A microtiter well, precoated with RANKL, would be used to capture denosumab in the samples. Assay buffer would be added to block as the plate is being covered with a plate sealer and shaken on a shaker. After washing, osteoprotegerin ligand conjugate normally is added. To ensure

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quality, a wash step is included in this method and results are then read. ICH Guidelines Prolia falls under ICH Guidelines Q5C, Q6B and Q1A to test the product's stability.

Guideline Q5C covers the overall quality of biotechnological products. On the other hand, ICH guidelines falling under section Q1A deal with Prolia's stability test procedures to take in account of Denosumab's special characteristics as well as to take API. Both of these guidelines overlap. Q6B sets " specifications for proteins...

which are derived from recombinant... cell cultures." These guidelines ensure that Prolia's quality is up to all federal requirements as well as boosting it up more so that since its guidelines are stricter, the company has a greater advantage at quality. FDA Checklist Prolia's main risks are presented in its cell cultures. Since CHO cultures are mammalian, they are much more susceptible to microbes. Any FDA inspector should test the master cell bank and working cell bank for any bioburdens. They should also check the conditions of storage and check traceability of documents.

In addition, batch records follow procedure and validation should prove accordingly. Furthermore, as an inspector, the National Institute of Health's Guidelines should be reviewed for Recombinant DNA Research to evaluate the level of containment appropriate for such large scale production. Any FDA inspector should ask to see and request a copy for all permits. They should review SOPs for the sampling, isolation, counting, and reporting of test results and obtain copies of these essential documents.