

Statement by The Alliance for Better Bone Health Regarding ACTONEL® (risedronate sodium) tablets and Cases of Osteonecrosis of the Jaw

The Alliance for Better Bone Health (Procter & Gamble Pharmaceuticals and sanofi-aventis U.S.) is committed to providing physicians and patients with accurate information regarding its medicines. This statement is intended to provide information in reference to inquiries concerning the osteoporosis medication Actonel, an oral bisphosphonate, and cases reported of osteonecrosis of the jaw (ONJ). The cases of ONJ in the literature were subsequently linked to the use of bisphosphonates, but no true cause and effect relationship has been established.

What is Osteonecrosis of the Jaw (ONJ)?

There is no established consensus definition of ONJ; however, it has been generally described to present as “exposed, necrotic bone in the maxillofacial region that has persisted for more than 8 weeks.” Bisphosphonate use has been associated with this condition, however, many other conditions may present with exposed bone which are not related to the use of bisphosphonates. (table 3) There not only is a need for clarification of the causal relationship between bisphosphonates and ONJ, but also the mechanism by which it could occur.

What are the signs/symptoms of ONJ?

ONJ affects the maxillofacial region and has been reported to be twice as common in the mandible versus the maxilla and even more common in areas where thin mucosa overly bony prominences.

A patient may identify a case of ONJ if they are experiencing the following typical signs/symptoms in the jaw:

- Pain
- Soft tissue swelling and infection (infection may or may not be present)
- Loosening of teeth
- Drainage
- Exposed bone

These symptoms can occur spontaneously, but more often occur after a dental procedure, such as a tooth extraction in the affected site or other trauma. Some cases of ONJ are asymptomatic and they may only become apparent after identification of exposed bone in the jaw. ONJ can also present similar to other dental or periodontal diseases, however differs in its lack of response to standard therapy.

What are the risks for developing ONJ?

The following factors MAY increase the risk of developing ONJ:

- Older age (>65 y/o)

- Dentoalveolar surgery
- Caucasian race
- Risk varies among different types of cancers
- Osteopenia/Osteoporosis with cancer diagnosis
- Clinically and radiographically apparent periodontitis
- Smoking
- Diabetes
- Alcohol use
- Poor oral hygiene
- Medications (chemotherapy, oral glucocorticoid use for chronic conditions, estrogen use)

IV versus Oral Therapy

- Most cases of ONJ that are associated with bisphosphonate use are in cancer patients on intravenous bisphosphonates, however some have been reported in patients using oral therapy.
- The condition appears to be less severe in patients receiving oral compared to IV bisphosphonates.

What are the numbers?

The number of cases of ONJ in the general population is unknown, but has been estimated to be fewer than 1,000. Among bisphosphonate users, the risk of ONJ is considerably lower in orally versus intravenously treated patients. Most cases of ONJ that are associated with bisphosphonate use are in cancer patients on intravenous bisphosphonates, however some have been reported in patients using oral therapy. The causative factor in these oral therapy cases has yet to be confirmed. The ability to prove a causal relationship is complicated by the presence of concomitant risk factors (ie., a history of IV bisphosphonate use, corticosteroid use, cancer and chemotherapy) in some of the reported post-marketing cases. In addition, the lack of sufficient clinical details in many of these reports makes it difficult to make definitive assessments, especially because a consensus definition of ONJ has yet to be established.

As of March 31, 2009, we estimate the reporting rate of osteonecrosis of the jaw associated with risedronate to be <2/100,000 patient-years exposure (<0.002%), without attribution of causation. Of the >15,000 patients monitored during risedronate phase III osteoporosis clinical trials, no observed cases of ONJ were identified. This was consistent with results of long-term toxicity and carcinogenicity nonclinical trials of multiple species (mouse, rat and dog). In addition, millions of patients have safely used risedronate since 1998.

What to do?

Actions that MAY reduce the risk of ONJ in patients about to begin or are currently on bisphosphonates:

- Maintain good oral hygiene
- Regular dental care

Bisphosphonate users should inform their dentist of their therapy. In addition, patients should report any oral problems to their dentist and physician.

If systemically plausible, it has been suggested that discontinuation of oral bisphosphonate therapy preceding and following elective invasive dental surgery may reduce the risk of ONJ in certain cases. There is no consensus on the duration of discontinuation. Because this approach remains to be validated and has not yet been supported by clinical evidence, each case should be reviewed individually taking into account the particular indication for the bisphosphonate, prior to discontinuing therapy. The prescribing physician and patient alike should be consulted prior to changes in therapy. The risks and benefits of a treatment decision should be used to formulate a clinical decision.

The Actonel Package Insert was revised in June 2005 and recently updated to include a precaution statement about ONJ and the use of bisphosphonates. The statement is a reflection of class labeling for all bisphosphonates. It states the following:

Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients taking bisphosphonates, including Actonel. Patients who develop ONJ while on bisphosphonate therapy should receive care by an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Clinical judgment of the treating physician and/or oral surgeon should guide the management plan (including the consideration of discontinuation of bisphosphonate therapy) of each patient based on individual benefit/risk assessment.

Osteoporosis occurs when the body loses bone at a rate faster than it can be replaced. As a result, bones become weaker, more brittle, and are more likely to break. Osteoporosis is most common in postmenopausal women. In the United States, an estimated 8 million women age 50 and over have osteoporosis and another 22 million are at risk of developing it. The most important goal of any osteoporosis therapy is to help prevent fractures.

When exercise and a diet rich in calcium and vitamin D aren't enough to help prevent osteoporosis-related fractures, a prescription medication such as Actonel® (risedronate sodium tablets) may be appropriate. Actonel can help make bones stronger and less likely to fracture.

There are some independent organizations that have published statements related to osteonecrosis of the jaw (ONJ). The Alliance for Better Bone Health provides these links below as they may be helpful to healthcare professionals in their efforts to learn more about ONJ. Note that The Alliance for Better Bone Health does not necessarily endorse the perspectives or opinions expressed within these sites.

American Dental Association

www.ada.org/prof/resources/topics/topics_osteonecrosis_bisphosphonate_report.pdf

National Osteoporosis Foundation

<http://www.nof.org/patientinfo/osteonecrosis.htm>

American Association of Oral and Maxillofacial Surgeons

www.aaoms.org/docs/position_papers/bronj_update.pdf

ASBMR

<http://www.jbmronline.org/doi/abs/10.1359/jbmr.0707ONJ>

