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**Informed Consent Relating to Risks  
Associated with Oral Bisphosphonate Use**

The following provides you with some additional information about dental treatment for patients taking oral bisphosphonates. Because you are taking a type of drug called a bisphosphonate, you may be at a small risk for developing osteonecrosis of the jaw and certain dental treatments may increase that risk. You should understand that the risk for developing this condition is very small.

**What are bisphosphonates?**

Bone is a living tissue with living cells and a blood supply. Every year your bone mass dies off and is replaced with new bone. Bisphosphonates reduce this bone cell turnover. Cells called osteoclasts naturally resorb bone, and then cells called osteoblasts lay down new bone. The average lifespan of an osteoclast is 14 days. Osteoclasts that ingest bisphosphonate die within 2 days. Intravenous/injected bisphosphonates, such as Zometa (zoledronate), Aredia (pamidronate) and the injectable form of Boniva (ibandronate) are primarily used in some type of cancer patients, reducing severe bone pain and even death. Oral (pill form) bisphosphonates, such as Fosamax (alendronate), Actonel (risedronate) and the oral form of Boniva (ibandronate), are heavily advertised and commonly prescribed for osteoporosis prevention. (Example: Fosamax entered the US market in 1995, and within 10 years, it became Merck's second best selling drug, with world-wide sales of \$3.2 billion in 2005, and over 22 million prescriptions written in the US alone, according to the drug research firm IMS Health. Fosamax was the first oral bisphosphonate to gain FDA approved and is the biggest seller in its class. Merck's SEC filing for the second quarter of 2006, reports Fosamax sales of \$821 million). It is estimated that 50% of intravenously/injected-administered bisphosphonate is bio-available and 50% excreted; the oral form is only 1% bioavailable and 99% excreted. So intravenous administration is 50 times more potent. Once bisphosphonates are absorbed in bone, they

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remain there for a long time. Most drugs have a half-life (the time it takes for the body to remove half of a bioavailable drug) measured in hours or days. Bisphosphonates become incorporated in bone and their half-life is over 11 years, regardless of the method of administration.

**What is osteonecrosis of the jaw?**

Osteonecrosis means death of bone, which can occur from the loss of the blood supply or by a problem with the bone's ability to regrow. Osteonecrosis of the jawbones has been associated with head and neck cancer radiation treatment (not routine x-rays). This form has been treatable with hyperbaric oxygen therapy.

Recently there have been cases of osteonecrosis of the jawbone in individuals taking bisphosphonates. In 2004 Ruggerio, et al first reported this in 63 patients they saw over 3 years with jawbone necrosis. 89% were taking intravenous bisphosphonates for cancer treatments, and 11% were taking oral bisphosphonates for treatment of osteoporosis or osteopenia. 1/4 of these cases involved no recent dental treatment; they occurred spontaneously. 3/4 of cases occurred after dental treatment or from denture sore spots. It is not known whether dental treatment caused the osteonecrosis of the jawbone, or exacerbated a pre-existing, sub-clinical osteonecrosis that did not yet become full blown.

**What is the risk for developing bisphosphonate osteonecrosis of the jaw (BONJ)?**

As of mid-2007, there are about 10,000 reported cases worldwide of BONJ related to bisphosphonates.

Your risk for developing osteonecrosis of the jaw (BONJ) from using IV (intravenous) bisphosphonates is very high. People who have had IV bisphosphonate therapy should avoid any elective oral surgery. BONJ in this population is not amenable to treatment.

Oral bisphosphonates, such as Fosamax, Actonel or oral Boniva are also related to a milder form of BONJ. If it does occur, it may be a serious condition with no successful treatment, so you should be aware of this rare complication. At this time, there is no way to precisely determine who will develop BONJ.

The following has been reported by Dr. Robert Marx of the University of Miami, a bone researcher and dental surgeon believed to be one of the world's leading authorities on the subject of BONJ. There are more cases of BONJ related to Fosamax

than Actonel. Marx theorizes that this may be because Fosamax is twice the milligram dosage of Actonel. The pill form of Boniva is too new to the market to compare to the other 2 medications. There has not been any reported case of BONJ in patients taking Fosamax or Actonel for less than 3 years. Also, there is a medical blood test, called a CTx test. Marx reports that he has never seen a case, and knows of no case, where BONJ developed where the pre-operative CTx results were over 150pg/ml. Therefore, anyone taking Fosamax, Actonel, or oral Boniva for 3 years or longer should have a CTx test done prior to any oral surgery and have a score over 150. Oral surgery should then be done with the patient off (no longer taking) Fosamax, Actonel or oral Boniva with the consent of their treating physician, only do one area of oral surgery at a time, and rinse with chlorhexidine 2 times per day for 2 months. If all is still uneventful (no BONJ) then another single area of oral surgery can be done using the same protocol, or Fosamax, Actonel or oral Boniva resumed if there is no further oral surgery to do.

BONJ is rare with oral bisphosphonates with perhaps only 1% of patients on oral bisphosphonates ever developing it. People who develop BONJ related to oral bisphosphonates must go off these medications to get their CTx score over 150 to have resolution. It is important for you to understand that other factors may play a role in the development of osteonecrosis, such as other medications you are taking and health problems that you may have. People on long-term steroid or methotrexate use, or have auto-immune disorders such as rheumatoid arthritis, in conjunction with oral bisphosphonates are at a much greater risk for developing BONJ than from taking oral bisphosphonate alone. Diabetics and smokers taking oral bisphosphonates are also at an increased, but lesser, risk than taking oral bisphosphonates alone. In addition, the longer a person takes oral bisphosphonates, the risk of developing BONJ, either thru dental surgery, a denture sore spot or tissue ulceration over the jaw bone, or just spontaneously developing it, goes up.

BONJ only occurs in jaw bones (upper and lower jaws....maxilla and mandible). It does not occur in other bones. It is theorized that this is because bone is resorbed (osteoclasts) and laid back down (osteoblasts) at 4 times the rate in the maxilla and 10 times the rate in the mandible than in long bones, like arms and legs.

### **Should I stop taking oral bisphosphonate?**

Typically oral bisphosphonates are prescribed for reducing the risk of bone fractures, especially hip fractures, in people with osteoporosis.

They are usually not prescribed for osteopenia. The benefits of reducing hip fractures and other complications associated with osteoporosis can be very important. It is estimated in one study that up to 10% of older, osteoporotic women that develop a hip fracture die within 2 years. Your dentist cannot advise you about these benefits. You should talk with your physician if you have any questions. There was a recent study in the Journal of the American Medical Association by Black published December 27, 2006, showed that osteoporosis patients taking Fosamax for 5 years and then going off for 5 years are at no greater risk of fractures than patients that stayed on Fosamax for the full 10 years. Your physician may not be aware of this recently published study, and may not be aware of BONJ related to oral bisphosphonates. Your physician can also discuss alternative medications used for osteoporosis, such as Forteo, Evista and Miacalcin. *It is imperative to remember that Dr. Sebastian is a licensed dentist, not a licensed physician, so this is given as information only, not as medical advise. Any decision to discontinue or change your oral bisphosphonate medication should only be done on the advise/consent of your treating physician.*

**What are the signs and symptoms of osteonecrosis of the jaw?**

You should tell your dentist immediately if you have any of the following symptoms, now or in the months following treatment:

- feeling of numbness, heaviness or other sensations in your jaw
- pain in your jaw
- swelling of your jaw
- loose teeth
- drainage
- exposed bone

It needs to be mentioned that many of the above are normal post-operative occurrences that go away in a short period of time, or may be strictly a “routine” dental problem

**Risks associated with not having the procedure.**

Your risk for developing osteonecrosis of the jaw is very small. You may also be at increased risk for developing other health problems if a dental disease is not treated. Active periodontitis is also associated with a significant increase in the risk of heart attacks, stroke and pregnancy complications and is well documented in the medical literature. In 2005, Marx reported the most common dental problem in patients with BONJ is existing active periodontitis (active gum disease). He also reports that people with healthy dental implants are at no higher risk of developing spontaneous BONJ because they have existing dental implants. Dental

implants to hold dentures in place may reduce the occurrences of denture sore spots, a contributing factor to spontaneous BONJ.

Your dentist(s) can discuss alternative treatments, other risks associated with various treatment options, and the risk of no treatment.

You should also consult with your treating physician about any medical health benefits and health risks associated with bisphosphonates.

### **Paget's disease**

Skelid (tiludronate) and Didronel (etidronate) are bisphosphonates used to treat Paget's bone disease. Their chemical structure differs. These bisphosphonates do not contain nitrogen in their chemical structure. Non-nitrogen containing bisphosphonates are nowhere near as potent as nitrogen containing bisphosphonates. These 2 drugs are rarely associated with BONJ.

It is important to remember that Paget's may also be treated with nitrogen-containing bisphosphonates, such as Zometa, Aredia, Actonel, Fosamax, Reclast and Boniva. These are associated with BONJ. It is not the disease you are treating that is associated with BONJ, it is the drug taken.

### **Bonefos**

Bonefos (clodronate) is a non-nitrogen containing bisphosphonate used to treat metastatic cancer to bones. Although it is a non-nitrogen containing bisphosphonate, it is very potent and there has been a case report of BONJ and Bonefos in the oral surgery literature. It is available in intravenous injection and in oral pills. It is not yet FDA approved in the US, although is approved in numerous countries since 1985.

### **Reclast**

Reclast (zoledronate) is a drug from Novartis recently approved by the FDA in August 2007. It is approved for a once a year IV infusion for osteoporosis and also for Paget's disease. There is no data on Reclast once a year infusions and BONJ. However, Reclast is identical to Zometa. According to Marx, Zometa is the worst offender for causing BONJ.

**Treatment of BONJ**

BONJ associated with IV bisphosphonates is more severe and is not amenable to treatment.

BONJ associated with oral bisphosphonates is generally less severe and may be amenable to treatment and resolution.

Any patient that would, by some chance, develop BONJ would be referred for treatment/management to an oral medicine specialist versed in BONJ. Dr. Sebastian has not had a case of BONJ and thus has no personal experience in its management.

**CTX test**

Measures the rate osteoclastic activity. Since Bisphosphonates kill osteoblasts, CTx scores will be lowered. We want a score over 150pg/ml to do oral surgery. A score over 150 does not guarantee you will not develop BONJ, but there are no reported cases where that has happened with pre-op CTx scores over 150. The test is a blood test, administered by Quest Diagnostics Laboratory. It requires a 12-hour fasting (nothing but water). It is drawn on Mondays, Wednesday and Fridays, as the blood vial is sent refrigerated overnight to San Juan Capistrano, where they run the tests every Tuesday, Thursday and Saturday. We must provide you with a lab requisition slip (lab work order).

Name \_\_\_\_\_

Signature \_\_\_\_\_

Date \_\_\_\_\_