

# Once-Yearly Reclast Approved for Osteoporosis

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The intravenous bisphosphonate zoledronic acid (Reclast) has been approved as the first treatment for postmenopausal osteoporosis that is administered once a year.

The approved dosage of zoledronic acid is a single 5-mg infusion given intravenously, over no less than 15 minutes, annually. The approval was announced in

August by the drug's manufacturer, Novartis Pharmaceuticals Corporation.

The 5-mg formulation of intravenous zoledronic acid was first approved earlier this year as a treatment for Paget disease. Zoledronic acid has been available in a 4-mg formulation (Zometa) for oncology indications, which is still available and should not be used in a patient taking Reclast.

Like other bisphosphonates, zoledronic acid inhibits osteoclast-mediated bone

resorption. Daily, weekly, or monthly dosing schedules for oral bisphosphonate drugs previously have been approved by the Food and Drug Administration. An injectable form of the bisphosphonate ibandronate (Boniva) is approved for use every 3 months for postmenopausal osteoporosis.

The average wholesale acquisition price for each zoledronic acid 5-mg dose is \$1,041.00, but the retail price may vary, a Novartis spokesperson said.

Approval for the osteoporosis indication was based on a 3-year, international study of more than 7,700 women with postmenopausal osteoporosis, the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial.

The study, which was published in May, found that women who received an annual 5-mg intravenous infusion of zoledronic acid had a 70% lower risk of vertebral fractures over a 3-year period, compared with women who were taking placebo.

Vertebral fracture occurred in 3.3% of the zoledronic acid group and 10.9% of the placebo group (N. Engl. J. Med. 2007;356:1809-22).

Hip fracture occurred in 1.4% of the zoledronic acid group and 2.5% of the placebo group, which represented a 41% reduction in the risk of hip fracture with active treatment.

Compared with placebo, zoledronic acid treatment also was associated with a significant reduction in nonvertebral fractures, clinical fractures, and clinical vertebral fractures, and significant improvements in bone mineral density and bone metabolism markers. These differences between groups were all statistically significant.

"Given the relatively poor adherence to oral bisphosphonate therapy in clinical practice, annual infusion of zoledronic acid may provide a promising approach to reducing fracture risk," the study authors concluded.

The study was supported by Novartis, and two authors were from Novartis.

"This is the first study where we have evidence for [a reduction in] spine, hip, and non-vertebral fractures all in the same trial," Dr. Nelson B. Watts, director of the University of Cincinnati Bone Health and Osteoporosis Center, said in an interview. Dr. Watts, one of the investigators in the trial, said that based on these efficacy data, he ranks this drug with the bisphosphonates alendronate (Fosamax) and risedronate (Actonel), which also have been shown to reduce the risks of these three significant fracture types.

Dr. Watts disclosed that he is a consultant to Novartis.

He attributes part of the drug's effectiveness to compliance. "Once the patients receive the dose, they have at least a year's worth of drug on board," he said, noting that one of the problems with treating silent diseases like osteoporosis is that a substantial proportion of patients stop taking the drug within 6-7 months of starting treatment for the disease.

Dr. Watts said that about one-third of patients have an acute phase response, with a fever, muscle aches, and other flu-like symptoms, but if they are premedicated with acetaminophen or ibuprofen, they are less likely to have those symptoms, or the symptoms, if they occur, are less severe.

This is also a first-dose phenomenon, so whether patients do or do not have these symptoms with the first dose, they are unlikely to experience the symptoms with subsequent doses, he added. ■

**SYNVISC**  
HYLAN G-F 20

UNIQUE NATIONAL  
HCPCS CODE

**Q4084**

#### BRIEF SUMMARY FOR THE PHYSICIAN (CONSULT PACKAGE INSERT FOR FULL PRODUCT INFORMATION)

**CAUTION:** Federal law restricts this device to sale by or on the order of a physician (or properly licensed practitioner).

**INDICATIONS** Synvisc is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics, e.g., acetaminophen.

**CONTRAINDICATIONS** • Do not administer to patients with known hypersensitivity (allergy) to hyaluronan (sodium hyaluronate) preparations. • Do not inject Synvisc in the knees of patients having knee joint infections or skin diseases or infections in the area of the injection site.

**WARNINGS** • Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation because hyaluronan can precipitate in their presence. • Do not inject Synvisc extra-articularly or into the synovial tissues and capsule. Local and systemic adverse events, generally in the area of the injection, have occurred following extra-articular injection of Synvisc. • Intravascular injections of Synvisc may cause systemic adverse events.

**PRECAUTIONS General** • The effectiveness of a single treatment cycle of less than three injections of Synvisc has not been established. • The safety and effectiveness of Synvisc in locations other than the knee and for conditions other than osteoarthritis have not been established. • Do not inject anesthetics or other medications into the knee joint during Synvisc therapy. Such medications may dilute Synvisc and affect its safety and effectiveness. • Use caution when injecting Synvisc into patients who are allergic to avian proteins, feathers, and egg products. • The safety and effectiveness of Synvisc in severely inflamed knee joints have not been established. • Strict aseptic administration technique must be followed. • **STERILE CONTENTS.** The syringe is intended for single use. The contents of the syringe must be used immediately after its packaging is opened. Discard any unused Synvisc. • Do not use Synvisc if package is opened or damaged. Store in original packaging (protected from light) at room temperature below 86°F (30°C). **DO NOT FREEZE.** • Remove synovial fluid or effusion before each Synvisc injection. • Synvisc should be used with caution when there is evidence of lymphatic or venous stasis in that leg.

**Information for Patients** • Provide patients with a copy of the Patient Labeling prior to use. • Transient pain, swelling and/or effusion of the injected joint may occur after intra-articular injection of Synvisc. In some cases the effusion may be considerable and can cause pronounced pain; cases where swelling is extensive should be discussed with the physician. • As with any invasive joint procedure, it is recommended that the patient avoid any strenuous activities or prolonged weight-bearing activities such as jogging or tennis following the intra-articular injection.

**Use in Specific Populations** • **Pregnancy:** The safety and effectiveness of Synvisc have not been established in pregnant women. • **Nursing mothers:** It is not known if Synvisc is excreted in human milk. The safety and effectiveness of Synvisc have not been established in lactating women. • The safety and effectiveness of Synvisc have not been established in children.

#### ADVERSE EVENTS

##### Adverse Events Involving the Injected Joint

**Clinical Trials:** A total of 511 patients (559 knees) received 1771 injections in seven clinical trials of Synvisc. There were 39 reports in 37 patients (2.2% of injections, 7.2% of patients) of knee pain and/or swelling after these injections. Ten patients (10 knees) were treated with arthrocentesis and removal of joint effusion. Two additional patients (two knees) received treatment with intra-articular steroids. Two patients (two knees) received NSAIDs. One of these patients also received arthrocentesis. One patient was treated with arthroscopy. The remaining patients with adverse events localized to the knee received no treatment or only analgesics.

**Postmarket Experience:** The most common adverse events reported have been pain, swelling and/or effusion in the injected knee. In some cases the effusion was considerable and caused pronounced pain. In some instances, patients have presented with knees that were tender, warm and red. It is important to rule out infection or crystalline arthropathies in such cases. Synovial fluid aspirates of varying volumes have revealed a range of cell counts, from very few to over 50,000 cells/mm<sup>3</sup>. Reported treatments included symptomatic therapy (e.g., rest, ice, heat, elevation, simple analgesics and NSAIDs) and/or arthrocentesis. Intra-articular corticosteroids have been used when infection was excluded. Rarely, arthroscopy has been performed. The occurrence of post-injection effusion may be associated with patient history of effusion, advanced stage of disease and/or the number of injections a patient receives. Reactions generally abate within a few days. Clinical benefit from the treatment may still occur after such reactions.

The clinical trials described above included 38 patients who received a second course of Synvisc injections (132 injections). There were two reports in nine patients (9.1% of injections, 23.7% of patients) of knee pain and/or swelling after these injections. Reports of two additional clinical trials in which patients received repeated courses of Synvisc treatment have appeared during the post-marketing period. One of these trials included 48 patients who received 210 injections during a second course of Synvisc treatment; the other contained 71 patients who received 211 injections during a second course of Synvisc treatment. A total of 157 patients have received 553 injections in the three clinical trials of repeated courses of Synvisc treatment. The reports in these trials describe a total of 48 reports of adverse events localized to the injected knee in 35 patients that occurred after injections that patients had received during their second course of treatment. These adverse events accounted for 6.3% of injections in 22.3%

of patients as compared to 2.2% of injections in 7.2% of patients in a single course of Synvisc injections. In addition, reports of two retrospective studies during the post-marketing period have described adverse events localized to the injected knee that have occurred after 4.4% and 8.5% of injections that patients had received during one or more repeated courses of Synvisc treatment.<sup>2,3</sup> Intra-articular infections did not occur in any of the clinical trials and have been reported only rarely during clinical use of Synvisc.

#### OTHER ADVERSE EVENTS

**Clinical Trials:** In three concurrently controlled clinical trials with a total of 112 patients who received Synvisc and 110 patients who received either saline or arthrocentesis, there were no statistically significant differences in the numbers or types of adverse events between the group of patients that received Synvisc and the group that received control treatments.

Systemic adverse events each occurred in 10 (2.0%) of the Synvisc-treated patients. There was one case each of rash (thorax and back) and itching of the skin following Synvisc injections in these studies. These symptoms did not recur when these patients received additional Synvisc injections. The remaining generalized adverse events reported were calf cramps, hemorrhoid problems, ankle edema, muscle pain, tonsillitis with nausea, tachyarrhythmia, phlebitis with varicosities and low back sprain.

**Postmarket Experience:** Other adverse events reported include: rash, hives, itching, fever, nausea, headache, dizziness, chills, muscle cramps, paresthesia, peripheral edema, malaise, respiratory difficulties, flushing and facial swelling. There have been rare reports of thrombocytopenia coincident with Synvisc injection. These medical events occurred under circumstances where causal relationship to Synvisc is uncertain. (Adverse events reported only in worldwide postmarketing experience, not seen in clinical trials, are considered more rare and are italicized.)

#### DETAILED DEVICE DESCRIPTION

Each syringe of Synvisc contains:

Hylan polymers (hylan A + hylan B) .....	16 mg
Sodium chloride .....	17 mg
Disodium hydrogen phosphate .....	0.32 mg
Sodium dihydrogen phosphate monohydrate .....	0.08 mg
Water for injection .....	q.s. to 2.0 mL

#### HOW SUPPLIED

Synvisc is supplied in a 2.25 mL glass syringe containing 2 mL Synvisc.  
Product Number: 58468-0090-1 3 disposable syringes  
The contents of the syringe are sterile and nonpyrogenic.

#### DIRECTIONS FOR USE

Synvisc is administered by intra-articular injection once a week (one week apart) for a total of three injections.

**Precaution:** Do not use Synvisc if the package has been opened or damaged. Store in original packaging (protected from light) at room temperature below 86°F (30°C). **DO NOT FREEZE.**

**Precaution:** Strict aseptic administration technique must be followed.

**Precaution:** Do not concomitantly use disinfectants containing quaternary ammonium salts for skin preparation because hyaluronan can precipitate in their presence.

**Precaution:** Remove synovial fluid or effusion before each Synvisc injection.

Do not use the same syringe for removing synovial fluid and for injecting Synvisc, but the same needle should be used.

Take particular care to remove the tip cap of the syringe and needle aseptically.

Twist the gray tip cap before pulling it off, as this will minimize product leakage.

Inject Synvisc into the knee joint through an 18 to 22 gauge needle.

To ensure a tight seal and prevent leakage during administration, secure the needle tightly while firmly holding the luer hub.

**Precaution:** Do not over tighten or apply excessive leverage when attaching the needle or removing the needle guard, as this may break the tip of the syringe.

Do not inject anesthetics or any other medications intra-articularly into the knee while administering Synvisc therapy. This may dilute Synvisc and affect its safety and effectiveness.

**Precaution:** The syringe containing Synvisc is intended for single use. The contents of the syringe must be used immediately after the syringe has been removed from its packaging. Inject the full 2 mL in one knee only. If treatment is bilateral, a separate syringe must be used for each knee. Discard any unused Synvisc.

This brief summary is based upon the current circular, 70230602, revised November 15, 2004.

**References:** 1. Raynaud JP, Bellamy N, Goldsmith CH, Tugwell P, Torrance GW, Pericak D, et al. (2002). An evaluation of the safety and effectiveness of repeat courses of hylan G-F 20 for treating patients with knee osteoarthritis. Osteoarthritis Research Society International, 2002 OARSI World Congress on Osteoarthritis, Sydney, Australia [Paper reference #PS128]. Presentation on File. 2. Leopold SS, Warme WJ, Pettis PD and Shott S. (2002). Increased frequency of acute local reaction to intra-articular Hylan G-F 20 (Synvisc) in patients receiving more than one course of treatment. *J Bone Joint Surg.* 2002;84-A(9): 1619-1623. 3. Waddell DD, Estey DJ and Bricker D. (2001). Retrospective tolerance of Hylan G-F 20 using fluoroscopically-confirmed injection and effectiveness of retreatment in knee osteoarthritis. Proceedings of the American College of Rheumatology Annual Meeting 2001. Presentation on File.

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