

# Versión Final

Illnesses and concomitant therapies, special care should be taken in the administration.

**ADVERSE REACTIONS:** Intravenous administration of zoledronic acid has been commonly associated with flu-like syndrome: Fever, chills, bone pain and/or arthralgias, and in most cases, no specific treatment is required and the symptoms subside within some hours or days. Occasionally, reactions such as nausea and vomiting have been reported. Occasionally local reactions at the infusion site such as redness or swelling were also observed. In most cases, no specific treatment is required and the symptoms subside after 24-48 hours. Rare cases of rash, pruritus, and chest pain have been reported following treatment with zoledronic acid. As with other bisphosphonates, cases of conjunctivitis and hypomagnesemia have been reported. Frequently, calcium renal excretion decrease is accompanied by a decrease in phosphate serum concentrations, which does not require treatment. The serum calcium may fall to asymptomatic hypocalcemic levels. Grade 3 increase for serum creatinine (common toxicity criteria) was observed in 2.3; 3.1, and 3.0 % of the patients treated with 4, 8 mg of zoledronic acid, and 90 m of sodium pamidronate, as expected for this stage of the disease and for this type of compounds. Some renal function damages were reported, but the causal relationship could not be established.

**Adverse reactions reported in clinical studies:**

**General:** Asthenia, chest pain, leg edema, mucositis.

**Digestive system:** Dysphagia.

**Hematic and lymphatic system:** granulocytopenia, thrombocytopenia, and pancytopenia.

**Infections:** non-specific infection.

**Laboratory abnormalities:** Hypocalcemia.

**Metabolic and Nutritional:** Dehydration

**Musculoskeletal:** Arthralgias, Osteonecrosis of the jaw.

**Nervous System:** Headache, somnolence.

**Respiratory system:** Pleural effusion.

**OVERDOSAGE:** There is no experience of acute overdose with zoledronic acid. Two patients received Zoledronic acid 32 mg over 5 minutes in clinical trials. Neither patient experienced any clinical nor laboratory toxicity. Overdosage may cause clinically significant hypocalcemia, hypophosphatemia, and hypomagnesemia. These disorders should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively. In controlled clinical trials, administration of zoledronic acid 4 mg as an intravenous infusion over 5 minutes has been shown to increase the risk of renal toxicity compared to the same dose administered as a 15 minute intravenous infusion. In controlled clinical trials, zoledronic acid 8 mg has been shown to be associated with an increased risk of renal toxicity compared to zoledronic acid 4 mg, even when given as a 15 minute intravenous infusion, and was not associated with added benefit in patients with hypercalcemia of malignancy. Single doses of zoledronic acid should not exceed 4 mg and the duration of the intravenous infusion should be no less than 15 minutes.

In case of overdose, go to the nearest Hospital

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**Information for Patients:** Zoledronic acid is a new and highly potent drug belonging to the group of substances known as bisphosphonates. They bind tightly to the bone and reduce the bone resorption rate. It is used to reduce the quantity of calcium in blood when it is extremely high due to the presence of a tumor. Tumors may accelerate bone remodeling, thus increasing bone calcium release. This condition is called hypercalcemia induced by tumors.

Ask your doctor if you have any doubt about this medicine and why he/she has prescribed it to you. Follow your doctor's instructions, since they may be different to the ones included in the package insert.

Do not administer zoledronic acid if:

You are sensible to zoledronic acid or other bisphosphonate (group of substances to which zoledronic acid belongs) or any of the components of Acido Zoledrónico Servycal. Ask your doctor if you have any doubts.

Before being administered zoledronic acid: Inform your doctor if you have any liver or renal condition.

**Pregnancy:** If you are pregnant or you are considering becoming pregnant, your doctor will explain the possible risks and benefits of administering zoledronic acid during pregnancy.

**Breast-feeding:** If you are breastfeeding, ask your doctor, since it is unknown if zoledronic acid is excreted in human milk.

**Use in the elderly:** No special cautions apply.

**Use in children:** Not recommended.

**Ability to drive and use machines:** There is no experience of the use of zoledronic acid in these cases. Caution should be exercised when performing these activities.

**Use of other medicines:** Tell your doctor what you are taking and what you have been taking recently.

If you have asthma or are allergic to aspirin.

Your doctor will check your response to therapy regularly, and will carry out blood analysis on a regular basis, especially during the initial phase of the therapy.

Call your doctor as soon as possible whenever any of the following adverse reactions occur:

Body temperature increase, chills, bone and/or muscle pain. In most cases they subside within some hours or days, and do not require specific treatment.

Gastrointestinal reactions such as nausea and vomiting.

Redness and swelling at infusion site, pruritus and chest pain. Isolated cases of conjunctivitis.

In blood tests, changes in renal function (such as creatinine increase) are observed. This changes may occur with other substances from this group. Some cases of renal diseases have been reported, but their causal relationship has not been clearly established.

It may result in breathlessness in patients with asthma or allergic to aspirin.

Serum concentrations of calcium, phosphate and/or magnesium may show a marked decrease; however, your doctor will take any necessary action to counteract it.

Call your doctor if you develop any unexpected adverse event.

**Therapy duration:** Usually, only one infusion of zoledronic acid is administered. Therapy may be repeated if necessary. Your doctor will decide how many infusions do you need and how often.

Presentation: Packed containing 1 vial with lyophilized powder and 1 ampoule with diluent.

Keep between 15 °C and 30 °C.

**KEEP OUT OF THE REACH OF CHILDREN.**

Medicinal Specialty authorized by Argentine Ministry of Health (ANMAT); Certificate No. 51.377

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Revision date: 09/2002



Quali-Quantitative Composition:

Each vial contains:

Zoledronic Acid Monohydrate (corresponding to 4.00mg zoledronic acid, anhydrous) ..... 4.264mg  
Mannitol ..... 220.000mg  
Sodium citrate ..... 24.000mg

Each ampoule diluent contains:

Sterile distilled water..... 5.0ml

**Therapeutic action:** Inhibitor of osteoclastic bone resorption. ATC Classification: M05BA 08.

**Indications:** Zoledronic acid is indicated for the treatment of tumor-induced hypercalcemia. A strong saline hydration and a therapy for hypercalcemia should be initiated without delay, and 2 liters/day of liquid should be administered to replace the excreted urine. Slight or asymptomatic hypercalcemia may be managed with traditional support measures (saline hydration, with or without Diuretics). Patients should be adequately hydrated during therapy; however, overhydration should be avoided in patients with cardiac failure. Diuretic therapy should only be initiated once hypovolemia is corrected. Safety and efficacy of zoledronic acid for hypercalcaemia associated with hyperparathyroidism or other condition unrelated to tumors have not been established.

**PHARMACOLOGICAL ACTION:**

**General:** Principal pharmacological action of zoledronic acid is bone resorption inhibition. Although it is not completely known the mechanism of action for the antiresorptive activity, it is believed that several factors contribute to this action. Zoledronic acid in vitro inhibits the activity of osteoclasts and induces their apoptosis. Zoledronic acid also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone. Zoledronic acid inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors.

**Pharmacokinetics:**

**Distribution:** Single 5-minute or 15-minute infusions of 2, 4, 8 or 16 mg of zoledronic acid were given to 32 patients with cancer and bone metastases. The post-infusion decline of zoledronic acid concentrations in plasma was consistent with a triphasic process, with population half-lives of T ½α 0.23 hours and T ½ β 1.75 hours, for distribution and rapid elimination, followed by a terminal elimination half-life of T ½ γ 167 hours, with low concentration in plasma within 28 days post infusion.

In vitro studies showed low affinity of zoledronic acid for the cellular components of human blood. Binding to human plasma proteins was approximately 22% and was independent of the concentration of zoledronic acid.

**Metabolism:** Zoledronic acid does not inhibit human P450 enzymes in vitro, shows no biotransformation. Zoledronic acid is not metabolized and is excreted unchanged via the kidney. The remainder is bound to bone tissue. From bone tissue it is released back into the circulation and eliminated via the kidney.

**Excretion:** In a study conducted in patients with cancer and bone metastasis, 44 ± 18 percent of zoledronic acid dose administered was recovered in urine within 24 hours, while the remainder presumably binds to bone tissue, and is slowly released back into the systemic circulation with a mean half-life of 167 hours. The area under the curve (plasma concentration vs. time) was linear in terms of the dose, and the accrued percentage of the excreted drug in 0-24 hour was independent of dose. Renal clearance (0-24 hours) in this population was of 4 ± 2.3 l/h, and plasma clearance representing renal elimination plus bone elimination, was of 5.6 ± 2.5 l/h. Zoledronic acid clearance is independent of dose, and is not affected by gender, age, race, and body weight. In a study in patient with cancer, increasing the a 4mg-dose infusion time from 5 to 15 minutes caused a 30% decrease in zoledronic acid concentration at the end of the infusion, and a 21% increase on the area under the plasma concentration versus time curve.

**Special Populations:** Pharmacokinetic data in patients with hypercalcemia are not available .

**Pediatric:** Pharmacokinetic data in pediatric patients are not available; therefore Zoledronic acid is not recommended.

**Geriatrics:** The pharmacokinetics of Zoledronic acid was not affected by the age in patients with cancer and bone metastases or whose age ranged from 40 to 85 years.

**Race:** The pharmacokinetics of Zoledronic acid was not affected by race in patients with cancer and bone metastases.

**Hepatic Insufficiency:** No clinical studies were conducted to evaluate the effect of pharmacokinetics of Zoledronic acid on patients suffering from hepatic impairment.

**Renal Insufficiency:** There are no pharmacokinetics data available for Zoledronic acid in patients with severe renal impairment. The studies conducted in patients with cancer and bone metastases who had a renal function ranging from normal to moderate creatinine clearance of 81 ± 30 ml/min (4.9 ± 1.8 l/h). Zoledronic acid renal clearance was found to be closely related to creatinine clearance. In average, the Zoledronic acid clearance in these patients was 82 ± 35 % of the creatinine clearance.

**Pharmacodynamics:** Clinical studies in patients with malignancy hypercalcemia showed that single-dose infusions of Zoledronic Acid are associated with decreases in serum calcium and phosphorus, and increases in urinary calcium and phosphorus excretion.

**DOSE AND ADMINISTRATION:** Consideration should be given to the severity of both the symptoms and the hypercalcemia-inducing tumor when considering use of Zoledronic acid. Vigorous saline hydration alone may be sufficient to treat mild, asymptomatic hypercalcemia. The maximum recommended dose of Zoledronic acid in malignancy hypercalcemia (albumin-corrected serum calcium 12 mg/dl or 3.0 mmol/l) is 4 mg and this dose must be given as a single-dose intravenous infusion over no less than 15 minutes.

Patients should be adequately rehydrated prior to administration. Retreatment with 8 mg can be given as an intravenous infusion over 15 minutes, may be considered for

patients that show a complete response (serum calcium normalization 2.7 mmol/l) and relapse or that are refractory to initial treatment. It is recommended that a minimum of 7 days elapse before retreatment to allow for full response to the initial dose. Renal function must be carefully monitored in all patients receiving Zoledronic acid and possible decline in renal function must be assessed prior retreatment (see Warnings and Precautions).

**Solution Preparation:** Each vial of Acido Zoledrónico Servycal is reconstituted with 5 ml of sterile water for injection, aseptically. Agitate until total dissolution.

To prepare a solution for infusion containing 8 mg Zoledronic acid, two 4 mg vials must be aseptically reconstitute by adding 5 ml of sterile water for injection to each of them, as described above. In both cases, the resulting solution must be diluted in 50 ml sodium chloride solution at 0.9% p/v or glucose solution at 5% p/v.

**Zoledronic acid must not be mixed with calcium-containing solutions such as Ringer solution.**

Reconstituted solution should be used immediately. Otherwise, storage prior to use is responsibility of the healthcare professional, and should be stored at 2 °C and 8 °C, and let the solution return to room temperature before administration. The time from reconstitution, to dilution and administration, should not exceed 24 hours in total.

Studies with glass bottles, as well as several types of infusion bags and infusion lines made from polyvinylchloride, polyethylene and polypropylene (prefilled with 0.9% w/v sodium chloride solution or 5% w/v glucose solution), showed no incompatibility with zoledronic acid.

**As data on the compatibility of zoledronic acid with other i.v. agent are not available, this medicine should not be mixed with other drugs or substances, and should always be administered by separate infusion lines.**

**NOTE:** Solutions for parenteral use should be visually inspected for particulate matter and discoloration prior to administration.

**CONTRAINDICATIONS:** This product is contraindicated in patients with clinically significant hypersensitivity to zoledronic acid, other bisphosphonates or any of the excipients in the formulation of Acido Zoledrónico Servycal.

**WARNINGS:** Due to the clinically significant risk of deterioration in renal function that may result in renal failure, a dose of zoledronic acid should not be higher than 4 mg administered over 15 minutes.

Bisphosphonates, including zoledronic acid, have been associated with renal toxicity, like renal function impairment and a potential renal failure. In the trials, the risk of renal deterioration (defined as a serum creatinine increase), has significantly increased in patients treated with zoledronic acid infused over 5 minutes, compared to those treated with the same dose infused over 15 minutes. In patients treated with 8 mg of zoledronic acid infused over 15 minutes, there is a marked increase of the risk for renal function impairment and renal failure. Renal function must be carefully monitored in all

patients receiving zoledronic acid by measuring renal function before treatment and periodically after treatment.

The following criteria should be applied in patients who repeat the therapy with zoledronic acid and those experiencing a decrease in renal function after therapy:

For patients with normal baseline serum creatinine before zoledronic acid administration, who experience an increase of 0.5 mg/dl within the two weeks following next dose, therapy is to be interrupted and resumed only when the creatinine level returned to within 10% of the baseline value.

For patients with normal baseline serum creatinine before zoledronic acid administration, who experience an increase of 1.0 mg/dl within the two weeks following next dose, therapy is to be interrupted and resumed only when the creatinine level returned to within 10% of the baseline value.

Potential risk of renal failure and subsequent doses of zoledronic acid should be appropriated evaluated with consideration given as to whether the potential benefit of treatment outweighs the possible risk.

**PRECAUTIONS**

**General:** After initiation therapy with zoledronic acid, serum levels of calcium, phosphate and magnesium, and particularly, serum creatinine should be monitored. If hypocalcemia, hypophosphatemia, or hypomagnesemia occur, supplemental therapy may be immediately instituted. Patients should be adequately hydrated prior to administration of zoledronic acid, and diuretics should not be used until patient is hydrated and should not be used in combination with zoledronic acid to avoid hypocalcemia.

**Renal failure:** Clinical data on zoledronic acid pharmacokinetics in patients with renal insufficiency are limited. Zoledronic acid is excreted via the kidney, and the risk of renal adverse reactions may be greater in patients with impaired renal function. Renal function should be closely monitored patients under therapy with Zoledronic acid.

Studies of zoledronic acid in the treatment of hypercalcemia of malignancy excluded patients with serum creatinine of 400 µmol/l or 4.5 mg/dl. There are no clinical and pharmacokinetic data available to select dose and schedules to ensure the use free of risks of zoledronic acid in patients with renal dysfunction, and it should only be used if possible benefits outweigh potential risks, and after considering other optional treatments.

In patients requiring repeated therapy for hypercalcemia of malignancy, serum creatinine levels should be evaluated prior to each dose. Patients with deterioration of renal function should be evaluated if possible benefits outweigh possible risks.

**Hepatic insufficiency:** Only limited data is available on the use of zoledronic acid in patients with hypercalcemia of malignancy with hepatic insufficiency, and these data are not enough to select the dose or ensure safe use in this population.

**Patients with asthma:** While not observed in clinical trials with zoledronic acid, administration of other bisphosphonates has been associated with bronchoconstriction in aspirin-sensitive asthmatic patients.

**Laboratory Tests:** Serum calcium, electrolytes, phosphate, magnesium, creatinine and CBC, hematonit/hemoglobin should also be monitored regularly in patients treated with zoledronic acid.

Effects on driving ability and machine operation: No studies on

the effects on the ability to drive and use machines have been performed; therefore, caution should be exercised when performing these activities.

**Drug interactions:** In vitro studies indicate that 22 ± 11 % of zoledronic acid binds to plasma proteins and in other in vitro studies also it does not inhibit Microsomal Enzymes of Cytochrome P450. Caution is advised when bisphosphonates are administered with aminoglycosides, since these agents may have an additive effect to lower serum calcium level for prolonged periods. Attention should also be paid to the possibility of hypomagnesemia developing during treatment. The concomitant use of zoledronic acid and anticancer agents, antibiotics and analgesics, did not resulted in evident clinical interactions. Caution should be exercised with the use concomitantly with diuretics due to an increase in the risk of hypocalcemia.

**Carcinogenesis:** Mice were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. There was an increased incidence of Harderian gland adenomas in males and females in all treatment groups (at doses of approximately 0.002 times a human intravenous dose of 4 mg, based on a comparison of relative body surface areas). Rats were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. No increased incidence of tumors was observed (at doses 0.2 times the human intravenous dose of 4 mg, based on a comparison of relative body surface area).

**Mutagenesis:** Zoledronic acid was not mutagenic in the mutagenicity assays.

**Teratogenesis:** Zoledronic acid was teratogenic in the rat at subcutaneous doses of approximately 0.2 mg/kg. Neither teratogenicity nor fetotoxicity in the rabbit, have been observed though maternal toxicity has.





**Impairment of fertility:** Female rats were given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day beginning 15 days before mating and continuing through gestation. Effects observed in the high-dose group included inhibition of ovulation and a decrease in the number of pregnant rats. Effects observed in both the mid-dose group and high-dose group included an increase in pre-implantation losses and a decrease in the number of implantations and live fetuses.

**Pregnancy:** Since the experience in the use of the drug during human pregnancy is limited, zoledronic acid should only be administered to pregnant women if the potential benefit of treatment outweighs the possible risk for the fetus.

**Breast-feeding:** It is not known whether zoledronic acid is excreted into human milk. It should not be used by breastfeeding women. It is worthy to mention, however, that bisphosphonates are poorly absorbed from the gastrointestinal tract, but also when they are excreted in milk, they are excreted by forming a bisphosphonate calcium complex that is not absorbed.

**Pediatric Use:** Safety and efficacy of zoledronic acid has not been established in children.

**Geriatric Use:** Clinical studies of zoledronic acid in hypercalcemia of malignancy included 34 patients who were 65 years of age or older. No significant differences in response rate or adverse reactions were seen in geriatric patients receiving zoledronic acid as compared to younger patients. Because decreased hepatic, renal, and cardiac function occurs more commonly in the elderly, and there are other concurrent

PRODUCTO: Acido Zoledrónico - Ingles - Prospecto		VERSION - 02	
COLORES	ALTERACIONES	Código Actual: 71024-02	 
 Pantone 194	<b>Emisión inicial:</b> Actualización de textos y nuevo DT.	Aprobado por:	Fecha
	Código anterior: 71024	Desarrollo de Packaging	
	Medida: 140 x 220 mm	Director Técnico	
	 Trazado	Garantía de Calidad	
Fuentes: <b>Frutiger Black Italic</b> – Arial (resto del texto)			