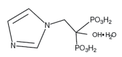
ACIDO ZOLEDRONICO KEMEX
Zoledronic Acid 4 mg
Lyophilized for Injection

FOR INTRAVENOUS USE
Made in Argentina Rx only

Formula
Each vial contains:
Zoledronic acid (as monohydrate).....4 mg
Mannitol.....220 mg
Sodium citrate.....24 mg
Each vial of solvent contains:
Water for injection.....5 ml

THERAPEUTIC ACTION
Inhibitor of osteoclastic bone resorption.
ATC Classification: M05BA 08

Structural and molecular formula:



C5H10N2O7P2.H2O

INDICATIONS
Tumor-induced Hypercalcemia:
Zoledronic acid is indicated for the treatment of tumor-induced hypercalcemia.
Vigorous saline hydration and hypercalcemia therapy should be promptly initiated and measures should be taken to restore the urine output to 2 L/day. Mild or asymptomatic hypercalcemia may be treated with conservative measures (saline hydration with or without loop diuretics). Patients should be hydrated adequately during treatment, but overhydration should be avoided in patients who have heart failure. Diuretic therapy should not be used before correction of hypovolemia. The safety and efficacy of zoledronic acid in the treatment of hypercalcemia associated with hyperparathyroidism or with other non-tumor-related condition have not been established.
Multiple Myeloma and Bone Metastases of Solid Tumors:
Zoledronic acid is indicated for the treatment of patients with multiple myeloma and with bone metastases of solid tumors in conjunction with standard antineoplastic therapy.

PHARMACOLOGY
General: The main pharmacological action of zoledronic acid is the inhibition of bone resorption. Although the mechanism of antiresorptive action is not fully understood, several factors are thought to contribute to this action. In vitro, zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis. Zoledronic acid also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone. Besides, zoledronic acid inhibits the increased osteoclastic activity and the bone calcium release induced by several stimulating factors released by tumors.
Pharmacokinetics:
Distribution: Single or multiple 5- or 15-minute infusions of zoledronic acid doses of 2, 4, 8 or 16 mg were administered to 64 patients with cancer and bone metastases. After the infusion, zoledronic acid concentrations decline in plasma in a triphasic process with half-lives of t ½α 0.24 hours and t ½β 1.87 hours, showing rapid distribution and elimination, followed by a terminal elimination phase with a half-life of t ½γ 167 hours and low concentrations in plasma within 28 days after infusion. The area under the plasma concentration versus time curve (AUC0-24h) was proportional from 2 to 16 mg of zoledronic acid.
In vitro studies showed low affinity of zoledronic acid for the cellular components of human blood. Protein binding is low, about 22%, and independent of the zoledronic acid concentration.
Metabolism: Zoledronic acid does not inhibit human cytochrome P450 enzymes in vitro and does not undergo biotransformation in vivo. Zoledronic acid is not metabolized and it is eliminated unchanged via the kidney. In animal studies, less than 3% of the administered intravenous dose was found in the feces, while the balance was recovered in the urine or taken up by bone, and eliminated unchanged via the kidney.
Excretion: In a study in 64 patients with cancer and bone metastases, 39 ±16% of the administered zoledronic acid dose was recovered in the urine within 24 hours, while the remainder corresponds to drug presumably bound to bone and is slowly released back into the systemic circulation with a half life of 167 hours. The area under the curve (plasma concentration versus time) was dose proportional and the cumulative percentage of drug excreted in 0-24 hours was independent of dose. The 0-24 hour renal clearance in these patients was 3.7 ±2.0 L/h and total body clearance was 5.6 ± 2.5 L/h. zoledronic acid clearance is independent of dose and is not affected by body weight, gender, age and race. In a study in cancer patients, increasing the infusion time of a 4-mg dose from 5 minutes (n=5) to 15 minutes (n=7) resulted in 34% decrease in zoledronic acid concentration at the end of infusion and 10% increase in the AUC.
Special Populations: There are no pharmacokinetic data available in patients with hypercalcemia.
Pediatrics: There are no pharmacokinetic data available in children; therefore, zoledronic acid is not indicated for use in these patients.
Geriatrics: The pharmacokinetics of zoledronic acid were not affected by age in patients with cancer and bone metastases whose ages range from 38 to 84 years old.
Race: The pharmacokinetics of zoledronic acid were not affected by race in patients with cancer and bone metastases.
Hepatic Impairment: There are no pharmacokinetic data available for zoledronic acid in patients with hepatic impairment.
Renal Impairment: There are no pharmacokinetic data available for zoledronic acid in patients with severe renal impairment. In studies in patients with cancer and bone metastases with normal renal function to moderate renal impairment and creatinine clearance of 81±30 mL/min (4.9 ± 1.8 L/ h), the renal clearance of zoledronic acid was found to be closely related to creatinine clearance. On average, the clearance of zoledronic acid in these patients was 82± 35% of the creatinine clearance.
Pharmacodynamics: Clinical studies in patients with tumor-induced hypercalcemia show that single-dose infusions lead to decreases in serum calcium and phosphorus and increases in urinary calcium and phosphorus excretion.
In patients with tumor-induced hypercalcemia and bone metastases, osteoclastic hyperactivity causes joint injury due to bone resorption.
Excessive release of calcium from bone into the blood results in polyuria and gastrointestinal disturbances, with progressive dehydration and decreased glomerular filtration rate. In turn, this results in increased renal reabsorption of calcium, triggering a cycle of worsening systemic hypercalcemia. Reduction of bone resorption and adequate fluid administration is essential to the management of tumor-induced hypercalcemia.
Patients who have tumor-induced hypercalcemia can be generally classified in two groups according to the physiopathologic mechanism: humoral hypercalcemia and hypercalcemia due to bone metastasis. In humoral hypercalcemia, osteoclasts and bone resorption are stimulated by factors synthesized by tumor cells that circulate systemically.
Invasion of bone by tumor cells may also produce hypercalcemia due to bone resorption by osteoclasts. Tumors commonly associated with this type of hypercalcemia include breast cancer and multiple myeloma.

DOSAGE AND ADMINISTRATION
Tumor-induced Hypercalcemia:
The severity as well as the symptoms of the tumor inducing hypercalcemia have to be taken into consideration when deciding on zoledronic acid dosing. Mild and asymptomatic hypercalcemia may be treated with vigorous saline hydration.
The maximum recommended dose of zoledronic acid in tumor-induced hypercalcemia (albumin-corrected serum calcium concentration ≥12.0 mg /dL or 3.0 mmol/L) is 4 mg, administered as a single-dose intravenous infusion over at least 15 minutes. Patients should be adequately hydrated prior to administration. Patients who achieve full response (normalization of serum calcium ≤ 2.7 mmol/L) and relapse or who are refractory to initial treatment, may be retreated with 8 mg of zoledronic acid given as a single-dose intravenous infusion over 15 minutes. However, at least 7 days should elapse before retreatment to allow for full response to initial dose.
Multiple myeloma and bone metastasis of solid tumors:
The recommended dose in patients with creatinine clearance > 60 mL/min is 4 mg of zoledronic acid administered as a 15-minute infusion every 3 to 4 weeks. The optimal duration of therapy is unknown.
The recommended doses for patients with reduced renal function (mild to moderate renal impairment) are listed in the following table:

Creatinine clearance (mL/min)	Recommended dose of zoledronic acid
> 60 mL/min	4.0 mg
50-60	3.5 mg
40-49	3.3 mg
30-39	3.0 mg

During treatment, the serum creatinine concentration should be measured before each zoledronic acid dose and treatment should be adjusted to avoid renal deterioration. (See Warnings and Precautions)
Patients should also be given an oral calcium supplement of 500 mg and 400 IU of oral vitamin D daily.
Preparation of Solution: Vials of Ácido Zoledrónico KEMEX must be aseptically reconstituted with 5 mL of sterile water for injection and shaken until total the powder is completely dissolved.
To prepare an infusion solution containing 8 mg of zoledronic acid, two 4-mg vials should be reconstituted aseptically by adding 5 mL of sterile water for injection as specified above.
The resulting solution should be diluted in 100 mL of 0.9% sodium chloride or 5% dextrose injection, w/v.
The reconstituted solution of zoledronic acid must not be mixed with solutions containing calcium such as the Ringer´s solution.
The prepared solution should be used immediately; otherwise, it should be kept until use by the health care professional, refrigerated between 2-8 °C. The refrigerated solution should be allowed to reach room temperature before administration. The total time between reconstitution, dilution and administration must not exceed 24 hours.
Studies conducted in glass vials, different types of infusion bags (pre-filled with 0.9% sodium chloride or 5% dextrose injection) and infusion lines of polyvinyl chloride, polyethylene and polypropylene did not show any incompatibility with zoledronic acid.
Because there no available data concerning the compatibility of zoledronic acid with other substances administered intravenously, zoledronic acid should not be mixed with other medicines/substances and it should be administered in a separate infusion line.
Due to the significant risk of deterioration of the renal function, single doses of zoledronic acid should not exceed 4 mg and the duration of intravenous infusion should be at least 15 minutes.

NOTE: Drugs for parenteral administration should be visually inspected before infusion and they should be discarded if particulate matter or discoloration is observed.

CONTRAINDICATIONS
Zoledronic acid is contraindicated in patients with hypersensitivity to the drug or other bisphosphonates or nay of the excipients of the composition.

WARNINGS
Due to the risk of clinically significant deterioration of renal function that may progress to renal impairment, single doses of zoledronic acid should not exceed 4 mg and the duration of infusion should at least 15 minutes.
Bisphosphonates, including zoledronic acid, have been associated with renal toxicity manifestations such as deterioration of the renal function and in some cases with renal impairment. In clinical trials, the risk of deterioration of the renal function (defined as an increase in serum creatinine) increased significantly in patients given zoledronic acid over 5 minutes compared to patients given the same dose over 15 minutes. In patients given 8 mg of zoledronic acid infused over 15 minutes, the risk of deterioration of the renal function and renal impairment is significantly increased.
•Patients receiving zoledronic acid should have their renal function assessed prior to zoledronic acid treatment and regularly monitored after treatment.
•The potential risk for renal impairment with subsequent zoledronic acid doses should be carefully assessed as against the potential benefits of treatment.
•Zoledronic acid is not recommended in patients with bone metastases and severe renal impairment.
•Pre-existing renal insufficiency and multiple cycles of zoledronic acid or other bisphosphonates are risk factors for renal function deterioration.
•Factors predisposing for renal deterioration, such as dehydration or the use of nephrotoxic drugs, should be identified and carefully managed, if possible.
•Zoledronic treatment in patients with tumor-induced hypercalcemia with severe renal impairment should only be considered after evaluating the risks and benefits of treatment.
•Dosage should be adjusted in patients with multiple myeloma and bone metastases of solid tumors if renal function deteriorates.
•Zoledronic acid should not be used during pregnancy due to the potential hazard to the fetus.
In studies in pregnant rats, pre- and post-implantation losses, decreases in viable fetuses, and fetal skeletal, visceral and external malformations were observed. No studies have been conducted in pregnant women.
•If the patient becomes pregnant during zoledronic acid treatment, the patient should be apprised of the potential hazards to the fetus. Women of childbearing potential should be warned about the potential risks in case they become pregnant.

PRECAUTIONS
General: Levels of calcium, magnesium and phosphate, as well as serum creatinine, should be monitored after the initiation of zoledronic acid treatment. If hypocalcemia, hypomagnesemia or hypophosphatemia occur, a supplemental therapy should be administered promptly.
Patients with tumor-induced hypercalcemia should be adequately hydrated before the administration of zoledronic acid. Loop diuretics should not be used until the patient is adequately hydrated and should be used with caution in combination with zoledronic acid in order to avoid hypocalcemia. Zoledronic acid should be used cautiously in combination with other nephrotoxic drugs.
Renal Impairment: Studies in connection with the use of zoledronic acid in patients with renal impairment are limited. Zoledronic acid is excreted unchanged by the kidney and the risk of renal adverse reactions may be greater in patients with renal impairment. Patients receiving zoledronic acid should have their renal function carefully monitored. Serum creatinine should be assessed before each dose of zoledronic acid.
Patients with serum creatinine ≥ 400 mol/L or 4.5 mg/ dL were excluded from studies of zoledronic acid in tumor-induced hypercalcemia. There are no clinical and pharmacokinetic data available to select dosage or rules to ensure the safe use of zoledronic acid in patients with renal impairment. Zoledronic acid should only be used if potential benefits outweigh the potential risks and after considering other treatment options. In patients requiring retreatment for tumor-induced hypercalcemia, serum creatinine levels should be assessed before each dose. In patients with renal function deterioration, a risk/benefit assessment should be made.
The following criteria should apply to patients who are retreated with zoledronic acid and who have decreased renal function after treatment:
•If patients have a normal serum creatinine level before zoledronic acid treatment but this level increases by 0.5% mg/dL within two weeks of the next dose, treatment should be discontinued until creatinine levels return to at least within 10% of the baseline value.
•If patients have a normal creatinine level before zoledronic acid treatment but this level increases by 1.0 mg/dL within two weeks of the next dose, treatment should be discontinued until creatinine levels return to at least within 10% of the baseline value.
Zoledronic acid is not recommended in patients with multiple myeloma and bone metastases of solid tumors, and an evidence of severe renal impairment.
Low doses of zoledronic acid should be given to patients with multiple myeloma and bone metastases of solid tumors, and an evidence of moderate renal impairment.
Treatment should be suspended in patients evidencing renal deterioration and it should be resumed only when serum creatinine returns to 10% of baseline value.
Hepatic Impairment: There are limited data available for the use of zoledronic acid in patients with tumor-induced hypercalcemia with hepatic impairment and these data are not adequate to select dosage or to ensure safe use of zoledronic acid in these patients.
Patients with Asthma: In clinical trials, bronchoconstriction associated with zoledronic acid administration was not reported, while bronchoconstriction was reported in aspirin sensitive patients receiving bisphosphonates.
Effects on the ability to drive vehicles and operate machinery: There are no data available to show how zoledronic acid treatment affects the ability to drive vehicles and operate machinery. Therefore, care should be exercised when performing these activities.
Osteonecrosis of the Jaw: In recent clinical trials, osteonecrosis of the jaw has been reported in cancer patients treated with bisphosphonates; some of them were receiving chemotherapy and corticosteroids. Most reports of ONJ were associated with invasive dental procedures such as extractions; some of them involved patients with signs of local infection including osteomyelitis. A dental examination by a dentist is recommended prior to treatment with zoledronic acid in patients with concomitant risk factors such as cancer, chemotherapy, corticosteroids therapy and poor oral hygiene.
While on zoledronic acid treatment, patients should avoid invasive dental procedures. Patients who develop ONJ during bisphosphonate treatment, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest that discontinuation of bisphosphonate treatment reduces the risk of ONJ.
Musculoskeletal Pain:
Severe and occasionally incapacitating bone, joint and/or muscle pain has been reported in patients treated with bisphosphonates. However, these reports have been infrequent.
The time to onset of symptoms varied from one day to several months after the initiation of zoledronic acid therapy. Most patients felt relief of symptoms after discontinuation of treatment. Some patients had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.
Laboratory Tests: Serum calcium, electrolytes, phosphates, magnesium, creatinine and CBC, and hematocrit/hemoglobin should be carefully monitored in patients treated with zoledronic acid.
Serum creatinine should be assessed prior to each dose of zoledronic acid.
Interactions: In vitro studies have shown the zoledronic acid is approximately 22% bound to plasma proteins. In vitro studies have also shown that zoledronic acid does not inhibit microsomal CYP450 enzymes. No in vivo drug interaction studies have beenperformed. However, caution should be exercised when bisphosphonates are administered with aminoglycosides since both agents have an additive effect resulting in lower serum calcium level for prolonged periods. Careful attention should be paid to avoid the development of hypomagnesemia during treatment. No clear clinical interactions have been reported with the concomitant administration of zoledronic acid and antineoplastic agents, antibiotics and commonly used analgesics. Special caution should be exercised when zoledronic acid is given in combination with diuretics due to an increased risk of hypocalcemia.
Carcinogenesis: In studies in mice and rats given oral doses of 0.1, 0.5 or 2.0 mg/kg/day, there was an increased incidence of Hardenian gland adenomas in females and males in all groups treated at doses 0.002 times the human intravenous dose of 4 mg and based on a comparison of relative body surface areas. In rats given doses 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 and based on a comparison of relative body surface areas.
Mutagenesis: Zoledronic acid was not genotoxic in mutagenicity assays.
Teratogenesis: Zoledronic acid is teratogenic in rats at subcutaneous doses ≥ 0.2 mg/kg. Teratogenicity and genotoxicity was not observed in rabbits, although there was evidence of maternal toxicity.
Impairment of Fertility: Female rats were given subcutaneous doses of zoledronic acid of 0.01, 0.03 or 0.10 mg/kg/day, starting 15 days before mating and continuing during gestation. In the high-dose group, inhibition of ovulation and decrease in the number of pregnant rats was observed. Effects observed in the mid-dose and high-dose groups included an increase in pre-implantation losses and a decrease in the number of implantations and live fetuses.
Pregnancy (category D): Since there are not adequate data on the use of zoledronic acid during human pregnancy, this drug should not be used in pregnant women unless the benefits for the patient outweigh the risks for the fetus.
Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The degree of incorporation of bisphosphonates into adult bones, and thus the amount available for release back into the systemic circulation, is directly related to the total dose and the duration of bisphosphonate use.
The impact of variables such as time between cessation of bisphosphonate therapy and conception, the bisphosphonate used and the route of administration (oral or intravenous) has not been established.
In female rats given doses of zoledronic acid of 0.01, 0.03 or 0.1 mg/kg/day starting 15 days before mating and continuing during gestation, the number of deaths and survival of newborns decreased in the mid-dose and high-dose groups.
Maternal mortality may be related to inhibition of skeletal calcium mobilization, resulting in post-partum hypocalcemia. This seems to be a bisphosphonate-type effect.
In pregnant rats given subcutaneous doses of zoledronic acid of 0.1, 0.2 or 0.4 mg/kg/day during gestation, adverse fetal effects were observed in the mid-dose and high-dose groups. These effects include: increase in pre- and post-implantation losses, decrease in viable fetuses, and skeletal, visceral and external malformations in the fetus.
Breastfeeding: Because it is unknown whether zoledronic acid is excreted in human milk, it should not be administered to breastfeeding women. However, bisphosphonates are not extensively absorbed by the gastrointestinal tract and, when they are excreted in milk, they do it in the form of a bisphosphonate-calcium complex that is not absorbed.
Pediatric Use: The safety and efficacy of zoledronic acid has not been established in children. Due to the long-term retention in bones, zoledronic acid should only be administered to children if potential benefits outweigh potential risks.
Geriatric Use: In clinical studies of zoledronic acid in tumor-induced hypercalcemia including 34 patients of 65 years of age or more, no significant differences in response or adverse reactions were found in elderly patients as compared to younger patients.
In clinical studies of zoledronic acid in patients with multiple myeloma and bone metastases of solid tumors aged over 65, similar safety and efficacy were revealed in older and younger patients.
However, since decreased hepatic, renal and cardiac function, as well as other diseases and therapies, is more common in elderly patients, care should be exercised when administering zoledronic acid to these patients.

ADVERSE REACTIONS
Following the intravenous administration of zoledronic acid, the most common adverse reactions are mild and transient, similar to those reported with the use of bisphosphonates.
Patients (approximately 9%) experienced a flu-like syndrome: fever, chills, bone pain and/or arthralgias, and myalgias. Occasionally, patients reported gastrointestinal reactions such as nausea and (5.8%) and vomiting (2.6%). Injection site reactions, such as redness or swelling, were infrequent (<1%). In most cases, no specific treatment is required and the symptoms subside after 24 or 48 hours. Rare cases of rash, pruritus and/or chest pain have been reported after zoledronic acid administration. As with other bisphosphonates use, conjunctivitis and hypomagnesemia (1%) have been reported.
Anorexia was reported in 1.5% of patients treated with zoledronic acid.
Generally, the reduction in calcium renal excretion is associated with decreased serum phosphate concentrations that require no treatment. Serum calcium may decrease until asymptomatic hypocalcemia levels.
Grade 3 creatinine increases (common toxicity criteria) were observed in 2.3%, 3.1% and 3.0% of patients treated with zoledronic acid 4 and 8 mg and pamidronate disodium 90 mg, respectively, as it was expected for this stage of the disease and with this type of compounds. Some cases of renal dysfunction have been reported; however, no causal relation could be established.
Based on placebo-controlled studies, severe anemia (Hb <8.0 g/dL) was reported in 5.2% of patients receiving zoledronic acid versus 4.2% of placebo-treated patients.
Adverse reactions reported in clinical trials:
The adverse reactions listed in Table 1 have been collected from clinical trials primarily following chronic treatment with zoledronic acid:

System / Organs	Frequency	Adverse Reaction
Hemic/Lymphatic	Common	Anemia
	Uncommon	Thrombocytopenia, leukopenia
	Rare	Pancytopenia
Nervous	Common	Headache
	Uncommon	Paresthesia, taste disturbance, hypothesia, hyperesthesia, tremor, dizziness.
Psychiatric	Common	Anxiety, sleep disorder.
	Uncommon	Confusion
Ocular	Common	Conjunctivitis
	Uncommon	Blurred vision
	Rare	uveitis, episcleritis
Gastrointestinal	Common	Nausea, vomiting, anorexia.
	Uncommon	Diarrhea, constipation, abdominal pain, dyspepsia, stomatitis, dry mouth.
Respiratory	Uncommon	Dyspnea, cough.
Skin and subcutaneous tissue	Uncommon	Pruritus, rash (including erythematous and macular rash), increased sweating.
Bone, connective tissue and musculoskeletal	Common	Bone pain, myalgia, arthralgia, generalized pain.
	Uncommon	Muscle cramps
Cardiovascular	Uncommon	Hypertension, hypotension.
	Rare	Bradycardia
Renal	Common	Renal damage
	Uncommon	Acute renal failure, hematuria, proteinuria .
Immune	Uncommon	hypersensitivity
	Rare	Angioneurotic edema
General Disorders	Common	Fever, flu syndrome.
	Uncommon	Asthenia, peripheral edema, injection site reaction, chest pain, weight gain.

Laboratory Abnormalities		
	Very common	Hypokalemia
	Common	Increased blood urea and creatinine levels.
	Uncommon	Hypomagnesemia. hypokalemia.
	Rare	Hyperkalemia, hypernatremia.

References:
- Very common: (≥1/10)
- Common: (≥1/100; <1/10)
- Uncommon: (≥1/1000; <1/100)
- Rare: (≥1/10.000; <1/1000)
- Very rare (<1/10000)

Atrial Fibrillation: In a randomized controlled clinical trial (3-year duration) evaluating the safety and efficacy of zoledronic acid (once a year) versus placebo in women with postmenopausal osteoporosis, the incidence of atrial fibrillation was 2.5% and 1.9% in the zoledronic acid 5 mg group and the placebo group, respectively. This imbalance has not been observed in other clinical trial of zoledronic acid in cancer patients given zoledronic acid 4 mg every 3-4 weeks. The mechanism that causing the increased incidence of atrial fibrillation is unknown. Therefore, if this adverse effect occurs, it should be reported.
Postmarketing adverse events:
Cases of osteonecrosis (primarily of the jaws) have been reported. Many of these patients had local infection including osteomyelitis and most reports occurred after extractions or other dental surgeries in cancer patients. Although causality has not been determined yet, it is recommended to avoid dental surgery.
There have been rare reports of hypotension leading to syncope or circulatory collapse, atrial fibrillation, somnolence, and bronchoconstriction.

OVERDOSAGE
There is no experience with acute overdosage of zoledronic acid. Two patients received 32 mg over 5 minutes in clinical trials. Neither patient experienced clinical nor laboratory toxicity. An overdose may cause clinically significant hypocalcemia, hypophosphatemia and hypomagnesemia; these disorders may be corrected by intravenous administration of calcium gluconate, sodium or potassium phosphate and magnesium sulfate, respectively.
In controlled clinical trials, the intravenous administration of zoledronic acid 4 mg over 5 minutes has been shown to increase the risk of renal toxicity compared to the same dose infused over 15 minutes. In controlled clinical trials, the administration zoledronic acid 8 mg has been shown to increase the toxicity risk compared to zoledronic acid 4 mg, even when given over 15 minutes, and it was not associated with additional benefits in patients with tumor-induced hypercalcemia.

Zoledronic acid 4 mg must be administered as a single-dose intravenous infusion over at least 15 minutes.

In the event of an overdose attend the nearest hospital or contact the Center for Toxicology.
Hospital de Niños Ricardo Gutiérrez.
Mark 011 if you live in the interior
(011) 4821-6666
Sánchez de Bustamante 1399 Capital Federal.
Specialty for adults:
Hospital Posadas.
Mark 011 if you live in the interior
(011) 4654-6648

Patient Information:
Zoledronic acid is a very strong medicine that belongs to a group of medicines called bisphosphonates. They bind strongly to the bone and reduce the rate of bone remodeling. Zoledronic acid is used to reduce the amount of calcium that is released into the blood when high levels of calcium in the blood are associated with malignancy. Malignancies may accelerate bone remodeling causing the release of calcium from the bone to be increased. This condition is known as tumor-induced hypercalcemia.
Ask your doctor if you have any question about this medicine or why you were prescribed this medicine.

Carefully follow your doctor´s instructions, which may be different from those contained in the patient package insert.
Zoledronic acid should not be used in the following cases:

If you are allergic to zoledronic acid or any other bisphosphonate (group of substances that includes zoledronic acid) or any of the components of Ácido Zoledrónico KEMEX. Ask your doctor if you have any doubt.
Before you are given zoledronic acid, tell your doctor if you have liver or kidney problems.
Pregnancy: If you are or may be pregnant, your doctor will explain the potential risks and benefits of zoledronic acid use during pregnancy.
Breastfeeding: If you are breastfeeding, tell your doctor. It is unknown whether zoledronic acid passes into breast milk.
Elderly people: No special precaution is required.
Children: zoledronic acid should not be used in children.
Operation of machinery: There are no data available to show how zoledronic acid treatment affects the ability to drive and operate machinery. Thus, you should be careful when performing these activities.
Other medicines: Tell your doctor if you are taking or have recently taken other medicines, and if you have asthma or you are allergic to aspirin.
Your doctor will check your progress at regular visits and will perform regular blood tests, especially at the early stages of treatment.
Check with your doctor as soon as possible if any of the following adverse reactions occur:
Increase of body temperature, chills and bone and/or muscle pain. In most cases these reactions subside in hours or days; no specific treatment is required.
Gastrointestinal reactions such as nausea and vomiting.
Redness or swelling of the skin at the injection site, pruritus and chest pain.
Rarely, conjunctivitis.
Blood tests show changes in renal function (increased creatinine); these changes may occur with other substances of this group. Some cases of renal disease have been reported; however, it is not clear whether they were caused by zoledronic acid use.
Zoledronic acid may cause difficulty breathing in patients with asthma or who are allergic to aspirin.
Your doctor will take the necessary actions if your blood calcium, phosphate and/or magnesium phosphate levels decrease too much.
Check with your doctor if any other unexpected adverse effect occurs.
Duration of treatment: Normally, only one infusion of zoledronic acid should be administered. Treatment may be repeated if necessary. Your doctor will decide how many infusions you need and how often.

HOW SUPPLIED
Carton containing 1 single dose vial of lyophilized powder and 1 vial of solvent.

STORAGE
Store at room temperature below 30°C.

"This medicine must be used exclusively under medical supervision and can not be repeated without any new medical prescription".

KEEP OUT OF REACH OF CHILDREN
MEDICAMENT AUTHORIZED BY THE MINISTRY OF HEALTH
CERTIFICATE N°. 56450

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Autonomous City of Buenos Aires - Argentina
Technical Director: Dr. Natalia Alonso – Pharmacist

05139.00

kemex laboratorio