DIVISIÓN ELEA	Producto: Simpla 5mg/100 ml Inyectable - DOSSIER	Código: 000000-00 reemplaza a -
	Material: Prospecto	Paises: LÍBANO
	Fecha: 17/04/19	Nº Diseño: 0588
Medidas: 180 x 280 mm	Plano:	Escala: 100%	Especif. Técnicas: ☐ LACA ☐ CUÑO ☐ BRAILLE
Nº Colores: 1	Citocromía ☐	Pantones: ■ Negro U	
NOTAS: ☐ El color representa al troquel. Los elementos representados con este color no deben imprimirse.		Cód. de barras: XXXXXXXXX
Motivo de emisión: Modifica Pie Legal ELEA/PHOENIX		

LOS COLORES QUE SE VEN EN ESTA IMPRESION PUEDEN TENER DESVIACIONES RESPECTO DE LOS COLORES PANTONE ESPECIFICADOS Y NO DEBEN USARSE COMO PATRON DE COMPARACION

Simpla®
Zoledronic Acid 5 mg / 100 ml

Injectable solution

MADE IN ARGENTINA
Sale Under Prescription

Formula:
Each 100 ml vial contains: Zoledronic acid 5.00 mg (as Zoledronic acid monohydrate 5.33 mg).
Excipients: Mannitol; Sodium citrate q.s. for pH: 6.5; Water for injection q.s. for 100 ml.

Therapeutic Action:
Antiresorptive. Inhibitor of bone resorption.

Indications:

Treatment of osteoporosis in postmenopausal women. Treatment to increase bone mass in men with osteoporosis. Prevention and treatment of glucocorticoid-induced osteoporosis in patients to be treated with glucocorticoids for at least one year. Treatment of Paget's bone disease in men and women.

Pharmacological features/Properties:

Pharmacological Action
The Zoledronic acid is an inhibitor of bone resorption which belongs to the group of nitrogenous bisphosphonates. It acts on the sites where bone resorption occurs. In the osteoclast, the site of action is the farnesyl-pyrophosphate-synthase enzyme, even though other sites should not be excluded.
Zoledronic Acid has been shown to be an inhibitor of bone resorption without affecting the mechanisms of bone formation and mineralization or the mechanical properties.

Pharmacokinetics
Absorption: The maximum plasma concentrations are reached immediately after the infusion. Once the infusion is finished, there is a fast fall and four hours after the administration of the intravenous infusion, the plasmatic concentration levels decrease at less than 10% of the maximum concentration. After 24 hours, the concentration decreases to less than 1% of the maximum level.
The increase of the infusion time from 5 to 15 minutes decreases by 30% Zoledronic acid concentration at the end of the infusion, but there have been no changes in the area under the plasma concentration-time curve.
Zoledronic acid administrated intravenously is cleared by a triphasic process; the rapid biphasic disappearance of the general circulation with 0.24 (1/2) and 1.87 (1/2 β) hour half-lives followed by a long phase with a terminal elimination half-life of 146 hours (1/2γ). After dosing every 28 days, accumulation of the active is not observed in plasma.
Metabolism and excretion: Zoledronic acid is not metabolized and it is excreted unchanged in the urine.
About 36% of the administered dose is recovered in urine during the first 24 hours. The rest remains retained in the osseous tissue and it is slowly released to the general circulation to be excreted in the urine.
Zoledronic acid is not metabolized by the body and it does not function as a metabolic inhibitor of cytochrome P450 enzymes.
Zoledronic acid fixation to plasmatic proteins is 56%; thus, pharmacological interactions with drugs of high percentage of protein binding are much unlikely.
Regardless of the individual characteristics (age, sex, body weight), total body clearance is 5.04 + 2.5 l/h.

Special Populations:
Kidney Disease: For patients with mild or moderate kidney disease it is not necessary to adjust the dose since no accumulation of Zoledronic acid is observed after the administration of multiple doses regardless of the renal function.
There have not been enough studies performed with patients with severe renal impairment, thus it is not advisable for these patients.

Posology and administration:
Treatment of osteoporosis in postmenopausal women. Treatment to increase bone mass in men with osteoporosis. Prevention and treatment of glucocorticoid-induced osteoporosis: 5 mg (1 vial of Simpla) administered by intravenous infusion during at least 15 minutes, once a year.
Prevention of osteoporosis in postmenopausal women: 5 mg (1 vial of Simpla) administered by intravenous infusion during at least 15 minutes, every 2 years.
Treatment of Paget's bone disease in men and women: 5 mg administered by intravenous infusion during at least 15 minutes. Patients with Paget's disease should receive 1500 mg of elemental calcium and 800 IU of vitamin D daily, especially during the 2 weeks following the administration of Simpla.
Simpla should be administered via intravenous infusion separately from any other medication. Avoid contact with solutions containing calcium or other divalent cations.

Instructions for use:
Simpla solution is to be used exclusively as intravenous infusion.
Simpla solution for intravenous infusion should not be administered or mixed with any other parenteral-administered drug.
SIMPLA, 100 mL IV infusion solution (5 mg Zoledronic acid) should be administered through a vented infusion line at constant rate. It should be administered during no less than 15 minutes.
Discard the remaining drug which was not used during the infusion prior to administration
Every parenteral administration product should be observed visually to control there are no particles and that it remains colorless
Do not use any parenteral product in which there are particles or if color has changed.

Contraindication:
SIMPLA is contraindicated in patients with known hypersensitivity to Zoledronic Acid or any of its excipients. Pregnancy. Breastfeeding. Hypocalcemia.

Warnings:
The patient should be properly hydrated before the administration of Simpla, especially those who are under treatment with diuretics.
Pre-existing hypocalcaemia must be treated with vitamin D and calcium before administering the infusion of Simpla. It should also be treated any other electrolytic disorder. The administration of Simpla should last no less than 15 minutes.
*Renal impairment: Not recommended in patients with severe renal insufficiency (creatinine clearance below 30 ml/min)
* Osteonecrosis of the jaw (ONJ): It has been reported predominantly in cancer patients treated with intravenous bisphosphonates (including Zoledronic acid), occurrence of osteonecrosis of jaw. Many of these patients were also receiving chemotherapy and corticosteroids. Most reported cases have been associated with dental procedures such as extractions. Many had signs of local infection, including osteomyelitis. Some cases occurred in patients with postmenopausal osteoporosis treated with intravenous or oral bisphosphonates.
Before initiating treatment with bisphosphonates should be considered the realization of a dental exam, taking appropriate preventive odontological measures in patients with accompanying risk factors (eg cancer, chemotherapy, corticosteroids, poor dental hygiene).
While duration of treatment and whenever possible, these patients should avoid bloody dental interventions. If patients develop osteonecrosis of jaw while receiving bisphosphonate therapy, dental surgery may exacerbate it. No data is available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis in patients requiring dental procedures. Each patient's treatment plan should be based on the clinical judgment of the treating doctor, after an individual assessment of the risks and benefits.

Precautions:
It is especially recommended that patients receive an adequate dose of calcium and Vitamin D, especially during the first 10 days after the administration of Simpla.
It is advisable to inform patients about the symptoms of hypocalcemia.
The doctor should monitor patients at risk of developing hypocalcemia.
Pregnancy: It should not be administered during pregnancy. Zoledronic acid may cause fetal damage if administered to pregnant women.
Not recommended for use in pregnant women, since there are no adequate and well controlled studies in women treated with Zoledronic acid. If the patient becomes pregnant while taking this medication, she should be alerted about the potential harm to the fetus. Women of childbearing age should be informed to avoid becoming pregnant during treatment with Simpla.

Breast-feeding:
It does not have any indications for breast-feeding women.
Its use is not recommended for breast-feeding women.

Drug Interaction: Because Zoledronic Acid is eliminated via renal, precautions are necessary when administered in association with drugs that significantly affect renal function such as diuretics and aminoglycosides. Zoledronic Acid does not affect cytochrome P450 enzymes in vitro.

Side Effects
After the administration of Simpla, like other intravenously administered bisphosphonates, the following symptoms are likely to develop:: flu-like syndrome, fever, headache, nausea, bone pain, myalgia, arthralgia. These symptoms have been observed in the first three days after administration, usually mild and transient, and most disappear on the fourth day. Swelling, redness and pain have been recorded in the injection sites after the administration of the infusion.
Postmenopausal osteoporosis:
In Phase III randomized double blind placebo-controlled HORIZON-PFT, clinical trial, which enrolled 7736 women (65- 89 years old), there were no significant differences in the general incidence of acute adverse events in contrast to placebo and most adverse events were mild and moderate. Zoledronic acid has been associated with the following post-administration symptoms: fever (18.1%), myalgia (9.4%), pseudo influenza symptoms (7.8%), arthralgia (6.8%) and headache (6.5%), most of them developed during the first 3 post-administration days. Most symptoms were of a mild and moderate nature and disappeared during the first 3 days after their development. The incidence of such symptoms decreased markedly with subsequent doses of Zoledronic acid. Paracetamol or ibuprofen administration reduces the incidence of post-dose symptoms developing within 3 days after Zoledronic acid administration.

The following are very frequent (>1/10), frequent (>1/100, <1/10), rare (>1/1.000, <1/100) and very rare (>1/1.000, <1/10.000) adverse reactions that the Investigator considers associated to Zoledronic acid 5 mg/100 ml in the assessment. The unwanted effects within each frequency group are presented regarding decreasing acuteness. Suspected adverse drug reactions (at least 1%) in **postmenopausal osteoporosis** in HORIZON-PFT clinical trial:
Nervous system disorders: Common: headache, dizziness. Infrequent: lethargy**, paresthesia, somnolence, tremor, syncope, dysgeusia..
Eye disorders: Infrequent: conjunctivitis, ocular pain, uveitis. Rare: episcleritis, iritis. Ear and labyrinth disorders: Uncommon: vertigo.
Respiratory, thoracic, and mediastinal disorders: Frequent: dyspnea *.
Gastrointestinal disorders: Common: nausea, vomiting, diarrhea. Infrequent: dyspepsia**, abdominal pain, dry mouth, esophagitis.
Skin and subcutaneous tissue disorders: Uncommon: rash. Musculoskeletal disorders: Common: myalgia, arthralgia, bone pain, back pain, pain in the extremities. Infrequent: joint swelling.
Renal and Urinary Disorders: Infrequent: increase of blood creatinine.

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Qualified Person
Laboratorio Elea Phoenix S.A.

General Disorders and Administration Site: Very common: fever. Common: Hypocalcemia *, flu-like symptoms***, chills, fatigue, asthenia, pain, discomfort, stiffness *. Uncommon: anorexia, peripheral edema, thirst.
#The incidence is based on the causality assessment made by the investigator and it includes the events which are more frequent than those which occur with placebo. In comparison with HORIZON-PFT clinical trial for postmenopausal women, the main deviations in adverse events in clinical trials on Paget's disease of bone are summarized as follows: * Frequent only in Paget's disease of bone. ** Frequent in Paget's disease of bone. *** Very frequent in Paget's disease of bone.
Class effects: renal impairment: Treatment with intravenous bisphosphonates – as Zoledronic acid – has been associated with the onset of renal impairment shown by an impairment of the renal function (i.e., an increase of plasma creatinine) and, in rare cases, by an acute renal impairment. Renal impairment has been observed following the administration of Zoledronic acid, mainly in patients with a pre-existing renal function involvement or with additional risk factors (for example, cancer patients receiving chemotherapy, concurrent nephrotoxic medications, acute dehydration), most of which received a 4 mg dose every 3-4 weeks, but is has also been seen in patients following a single administration. Patients with baseline creatinine clearance <30ml/min, test by urine dipstick = protein 2+ or increase in serum creatinine >0,5mg/dl during screening. In this study, change in creatinine depuration (determined annually before administration) and the incidence of renal impairment and renal damage were similar between groups treated with Zoledronic acid 5ml/100ml and those who received placebo for 3 years. A transient plasma creatinine increase was observed during the first 10 days post administration in 1.8% patients treated with Zoledronic acid 5mg/100mL versus 0.8% of those who received placebo.
Atrial fibrillation: In the three year study in which postmenopausal women with osteoporosis diagnosis were enrolled (HORIZON PFT), the general incidence of atrial fibrillation was low: they were reported as serious adverse events in 2.5% patients (96 out of 3862) in the 5 mg/100 mL Zoledronic acid group versus 1.9% patients (75 out of 3852) in the placebo group. They were reported as adverse events in 1.3% patients (50 out of 3862) in the 5mg/100mL Zoledronic acid group versus 0.4% patients (17 out of 3852) in the placebo group. This incidence has not been observed in other clinical trials with Zoledronic acid conducted out of Horizon program.
Laboratory Results: in HORIZON-PFT trial, about 0.2% patients had a significant decrease in plasma calcium concentration (lower than 1.87mmol/l) after the administration of 5mg/100mL Zoledronic acid. No cases of symptomatic hypocalcemia were observed. In Paget's disease of bone trials, symptomatic hypocalcemia was observed in 1% patients, with regression in all the cases.
Local Reactions: following the administration of Zoledronic acid, local reaction on the infusion site (0.7%) such as redness, swelling or pain were reported in 0.5% patients receiving placebo. Osteonecrosis of the Jaw: cases of osteonecrosis (mainly of the jaw) have been mainly reported in cancer patients treated with bisphosphonates, including Zoledronic acid (infrequent). Many of these patients had signs of local infection, even osteomyelitis, and most reports refer to cancer patients who had had dental extractions or other type of dental surgical procedure. The osteonecrosis of the jaw has many well documented risk factors, including cancer diagnosis, concurrent treatments (e.g., chemotherapy, radiotherapy, corticosteroids) and concurrent diseases (e.g., anemia, coagulopathy, infection, pre-existing oral disease). Although the causal link has not been determined, it is advisable to avoid dental surgery for recovery could be extended. In HORIZON-PFT trial, which enrolled 7736 patients, the occurrence of ONM in 1 patient treated with 5mg/100mL Zoledronic acid and 2 patients treated with placebo has been reported. The 3 cases had a remission.
Prevention of clinical fractures after a hip fracture: in HORIZON-RFT trial, most adverse events were mild or moderate and it was not necessary to discontinue the treatment. The incidence of acute adverse events was 38% in 5mg/100mL Zoledronic acid group and 41% in the placebo group. The adverse reactions presumably associated to Zoledronic acid in men and women with hip fracture in study Horizon-PFT are described bellow (in the investigator's judgment):
The causality assessment done by the investigator includes those events which occurred more frequently than with placebo.
The events are classified according to the following convention:
very frequent (>1/10)
frequent (>1/100, <1/10)
infrequent (>1/1.000, <1/100)
rare (>1/10.000,<1/1.000).
Psychiatric disorders: Infrequent: insomnia.
CNS disorders: Infrequent: headache.
Respiratory disorders: Infrequent: dyspnea.
Gastrointestinal disorders: Frequent: Nausea; Infrequent. Vomit, diarrhea, xerostomia, dental pain.
Skin and subcutaneous tissue disorders: Infrequent: Hyperhidrosis, itching, rash.
Musculoskeletal and connective tissue disorders: frequent: myalgia, bone pain, arthralgia. Infrequent: back pain, joint swelling, and musculoskeletal pain.
General disorders and administration site conditions: Frequent: fever, chills, asthenia. Infrequent: fatigue, pain, general discomfort, pseudo influenza symptoms, peripheral edema

Overdose:
Clinical experience with Zoledronic acid solution acute overdose is limited. Patients who received doses higher than the recommended ones should be closely monitored. Overdose may cause clinically significant renal impairment, hypocalcemia, hypophosphatemia and hypomagnesemia. Reductions of clinically relevant calcium, phosphorus and magnesium serum levels should be corrected by the intravenous administration of calcium gluconate, potassium or sodium phosphate and magnesium sulphate, respectively.
IN CASE OF AN OVERDOSE, GO TO THE NEAREST HOSPITAL OR CALL THE TOXICOLOGY CENTERS:

Storage Conditions:
Keep between 15° C and 30° C in its original package. Once open, it should be administered immediately.

Presentation
Package containing one 100 ml vial which contains 5 mg Zoledronic acid.

KEEP THIS AND OTHER MEDICINES OUT OF CHILDREN REACH.

Medicinal product authorized by the Ministry of Health.
Certificate Nº: 55.124.
PLH Laboratorio Elea Phoenix S.A., Av. Gral. Lemos Nº 2809,
Los Polvorines, Pcia. de Bs. As., Argentina.
Technical Director: Alfredo J. Boccardo, Pharmacist.
Manufactured by GEMEPE S.A., Lamadrid 1383/85, Bs. As., Argentina.

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Laboratorio
ELEA PHOENIX

NOELIA CLAUDIA VIZZI
[redacted] Qualified Person
Laboratorio Elea Phoenix S.A.

	Diseñador Gráfico	Desarrollo Packaging	Garantía de la calidad (Fla./Cons.)	Control Comercial (Nacionales)	Control Comercial (Exportaciones)	Control Médico (Dir. Médica)	Desarrollo Galénico (Fórmula)	Control de Marcas (Marcas/Patentes)	Control Regulatorio (Nacionales)	Control Regulatorio (Exportaciones)	Aprobación Final (Dir. Técnica)	Control archivo Final
Fecha												
Firma												
Aclaración (Completa)	Solange Mosquera											
Observaciones												

CADA CONTROL DEBERÁ REALIZARSE EN UN PLAZO NO MAYOR A 2 DÍAS HÁBILES