SEACROSS ZOLEDRONIC ACID SEACROSS 5 MG/100ML SOLUTION FOR INFUSION

NAME OF THE MEDICINAL PRODUCT
Seacross Zoledronic Acid 5 mg/100ml solution for infusion

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial with 100 ml of solution contains 5 mg zoledronic acid (as monohydrate).
Each ml of the solution contains 0.05 mg zoledronic acid anhydrous (as monohydrate)

PHARMACEUTICAL FORM
Solution for infusion
Clear and colourless solution.
pH: 5.50-7.00

PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: Drugs for treatment of bone diseases, bisphosphonates, ATC code: M05BA08

Mechanism of action

Zoledronic acid belongs to the class of nitrogen-containing bisphosphonates and acts primarily on bone. It is an inhibitor of osteoclast-mediated bone resorption.

Pharmacodynamic effects

The selective action of bisphosphonates on bone is based on their high affinity for mineralised bone. The main molecular target of zoledronic acid in the osteoclast is the enzyme farnesyl pyrophosphate synthase. The long duration of action of zoledronic acid is attributable to its high binding affinity for the active site of farnesyl pyrophosphate (FPP) synthase and its strong binding affinity to bone mineral.

Zoledronic Acid treatment rapidly reduced the rate of bone turnover from elevated post-menopausal levels with the nadir for resorption markers observed at 7 days, and for formation markers at 12 weeks. Thereafter bone markers stabilised within the pre-menopausal range. There was no progressive reduction of bone turnover markers with repeated annual dosing.

PHARMACOKINETIC PROPERTIES
Distribution

After initiation of the zoledronic acid infusion, plasma concentrations of the active substance increased rapidly, achieving their peak at the end of the infusion period, followed by a rapid decline to < 10% of peak after 4 hours and < 1% of peak after 24 hours, with a subsequent prolonged period of very low concentrations not exceeding 0.1% of peak levels.

Elimination

Intravenously administered zoledronic acid is eliminated by a triphasic process: rapid biphasic disappearance from the systemic circulation, with half-lives of $t_{½}a$ 0.24 and $t_{½}b$ 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of $t_{½}\gamma$ 146 hours. There was no accumulation of the active substance in plasma after multiple doses given every 28 days. The early disposition phases (α and β, with $t_{½}$ values above) presumably represent rapid uptake into bone and excretion via the kidneys.

Zoledronic acid is not metabolised and is excreted unchanged via the kidney. The administered dose is recovered in the urine, while the remainder is principally bound to bone tissue. This uptake into bone is common for all bisphosphonates and is presumably a consequence of the structural analogy to pyrophosphate. As with other bisphosphonates, the retention time of zoledronic acid in bones is very long. From the bone tissue it is released very slowly back into the systemic circulation and eliminated

via the kidney. The total body clearance is independent of dose, and unaffected by gender, age, race or body weight.

Special populations

Renal impairment

The renal clearance of zoledronic acid was correlated with creatinine clearance. The use of Zoledronic Acid in patients with severe renal impairment (creatinine clearance < 35 ml/min) is contraindicated due to an increased risk of renal failure in this population.

THERAPEUTIC INDICATIONS

- Treatment of osteoporosis
  - in post-menopausal women to reduce the incidence of hip, vertebral and non-vertebral fractures,
  - in men

at increased risk of fracture, including those with a recent low-trauma hip fracture.

- Treatment and prevention of osteoporosis associated with long-term systemic glucocorticoid therapy in post-menopausal women and in men at increased risk of fracture.

- Prevention of osteoporosis in post-menopausal women at increased risk of fracture.

- Treatment of Paget's disease of the bone.

POSOLOGY AND METHOD OF ADMINISTRATION

For the treatment of postmenopausal osteoporosis and osteoporosis in men, the recommended dose is a single intravenous infusion of 5 mg infusion of Seacross Zoledronic acid administered once a year.

For the treatment and prevention of glucocorticoid-induced osteoporosis in women and men, the recommended dose is a single intravenous infusion of 5 mg infusion of Seacross Zoledronic acid administered once a year.

In patients with a recent low-trauma hip fracture, it is recommended to give Seacross Zoledronic acid infusion two or more weeks after hip fracture repair. A loading dose of 50,000 to 125,000 IU of vitamin D given orally or via the intramuscular route is recommended prior to the first Seacross Zoledronic acid infusion.

For the prevention of osteoporosis in postmenopausal women, the recommended dose is a single intravenous infusion of 5mg Seacross Zoledronic acid administered once every 2 years.

For the treatment of Paget's disease the recommended dose is a single intravenous infusion of 5 mg Seacross Zoledronic acid.

Retreatment of Paget's disease: Specific retreatment data are not available. After a single treatment with Seacross Zoledronic acid in Paget's disease, an extended remission period is observed in responding patients.

Seacross Zoledronic acid (5 mg in 100 mL ready to infuse solution) is administered intravenously via a vented infusion line, given at a constant infusion rate. The infusion time must not be less than 15 minutes.

Patients must be appropriately hydrated prior to administration of Seacross Zoledronic acid. This is especially important for patients receiving diuretic therapy.

Adequate calcium and vitamin D intake is important in patients with osteoporosis if dietary intake is inadequate.

Elevated bone turnover is a characteristic of Paget's disease of bone. It is strongly advised that patients with Paget's disease receive the recommended daily allowance of supplemental calcium and vitamin D and this should be ensured during the initial 10 days following Seacross Zoledronic acid administration.

The incidence of post-dose symptoms occurring within the first three days after administration of Seacross Zoledronic acid can be reduced with the administration of paracetamol or ibuprofen shortly following Seacross Zoledronic acid administration..

Special populations
Patients with renal impairment
The use of Seacross Zoledronic Acid in patients with creatinine clearance < 35 ml/min is contraindicated (see section Contraindications and Warning and Precautions). No dose adjustment is necessary in patients with creatinine clearance ≥ 35 ml/min.

Patients with hepatic impairment
No dose adjustment is required.

Geriatric people (≥ 65 years or above)
No dose adjustment is necessary since bioavailability, distribution and elimination were similar in elderly patients and younger subjects.

Paediatric population
Seacross Zoledronic Acid is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy.

Method of administration
Intravenous use.
For single use only. Any unused solution should be discarded. Only clear solution free from particles and discoloration should be used.
Zoledronic Acid must not be mixed or given intravenously with any other medicinal product and must be given through a separate vented infusion line at a constant infusion rate. The infusion time must not be less than 15 minutes. Zoledronic Acid must not be allowed to come into contact with any calcium-containing solutions. If refrigerated, allow the refrigerated solution to reach room temperature before administration. Aseptic techniques must be followed during preparation of the infusion. The infusion must be conducted according to standard medical practice

CONTRAINDICATIONS

- Hypersensitivity to the active substance, to any bisphosphonates or to any of the excipients.
- Patients with hypocalcaemia.
- Severe renal impairment with creatinine clearance < 35 ml/min.
- Pregnancy and breast-feeding.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
General
The dose of 5 mg zoledronic acid must be administered over at least 15 minutes.

Seacross Zoledronic acid contains the same active ingredient found in Zometa (zoledronic acid), used for oncology indications, and a patient being treated with Zometa should not be treated with Seacross Zoledronic acid.

Patients must be appropriately hydrated prior to administration of Seacross Zoledronic acid. This is especially important in the elderly and for patients receiving diuretic therapy.

Pre-existing hypocalcaemia must be treated by adequate intake of calcium and vitamin D before initiating therapy with Seacross Zoledronic acid (see section CONTRAINDICATIONS). Other disturbances of mineral metabolism must also be effectively treated (e.g. diminished parathyroid reserve; thyroid surgery, parathyroid surgery, intestinal calcium malabsorption). Physicians should consider clinical monitoring for these patients.

Renal function

The use of Seacross Zoledronic acid in patients with severe renal impairment (creatinine clearance < 35 ml/min) is contraindicated due to an increased risk of renal failure in this population.
Renal impairment has been observed following the administration of Seacross Zoledronic acid, especially in patients with pre-existing renal dysfunction or other risks including advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy, or dehydration occurring after Seacross Zoledronic Acid administration. Renal impairment has been observed in patients after single administration. Renal failure requiring dialysis or with a fatal outcome has rarely occurred in patients with underlying renal impairment or with any of the risk factors described above.

The following precautions should be taken into account to minimise the risk of renal adverse reactions:

- Creatinine clearance should be calculated (e.g. Cockcroft-Gault formula) before each Seacross Zoledronic Acid dose. Transient increase in serum creatinine may be greater in patients with underlying impaired renal function; interim monitoring of serum creatinine should be considered in at-risk patients.
- Seacross Zoledronic Acid should be used with caution when concomitantly used with other medicinal products that could impact renal function.
- Patients, especially elderly patients and those receiving diuretic therapy, should be appropriately hydrated prior to administration of Seacross Zoledronic Acid.
- A single dose of Seacross Zoledronic Acid should not exceed 5 mg and the duration of infusion should not be less than 15 minutes.

Calcium and Vitamin D supplementation

Treatment and prevention of Osteoporosis

Adequate supplemental calcium and vitamin D intake is important in men and women with osteoporosis or treated to prevent postmenopausal osteoporosis if dietary intake is inadequate.

Prevention of Clinical Fractures after a Hip Fracture

Supplemental calcium and vitamin D intake is recommended for patients treated to prevent clinical fractures after a hip fracture.

Treatment of Paget's disease of bone

Elevated bone turnover is a characteristic of Paget's disease of bone. Due to the rapid onset of effect of zoledronic acid on bone turnover, transient hypocalcaemia, sometimes symptomatic, may develop and is usually maximal within the first 10 days after infusion of Seacross Zoledronic Acid (see section ADVERSE DRUG REACTIONS). Adequate vitamin D intake is recommended in association with Seacross Zoledronic Acid administration. In addition, it is strongly advised that adequate supplemental calcium corresponding to at least 500 mg elemental calcium twice daily is ensured in patients with Paget's disease for at least 10 days following Seacross Zoledronic Acid administration. Patients should be informed about symptoms of hypocalcaemia. Physicians should consider clinical monitoring for patients at risk.

Musculoskeletal pain

Severe and occasionally incapacitating bone, joint, and/or muscle pain have been infrequently reported in patients taking bisphosphonates, including Seacross Zoledronic Acid.

Osteonecrosis of the jaw (ONJ)
Osteonecrosis of the jaw has been reported predominantly in cancer patients treated with bisphosphonates, including zoledronic acid. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis. A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, anti-angiogenic drugs, corticosteroids, poor oral hygiene). During treatment with zoledronic acid, it is prudent to maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms. While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. The clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Osteonecrosis of other bones
Cases of osteonecrosis of other bones (including femur, hip, knee and humerus) have also been reported; however, causality has not been determined in the population treated with Seacross Zoledronic Acid.

Osteonecrosis of the external auditory canal
Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

Atypical fractures of the femur
Atypical subtrochanteric and diaphyseal femoral fractures have been reported in association with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain weeks to months before a completed femoral fracture.

Fractures are often bilateral; therefore, the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending an individual benefit risk assessment. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.
During bisphosphonate treatment, including Seacross Zoledronic Acid, patients should be advised to report any thigh, hip or groin pain and any patient with such symptoms should be evaluated for possible femur fracture.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Zoledronic acid is not systemically metabolized and does not affect human cytochrome P450 enzymes. Zoledronic acid is not highly bound to plasma proteins (approximately 43-55% bound) and interactions resulting from displacement of highly protein-bound drugs are therefore unlikely.

Zoledronic acid is eliminated by renal excretion. Caution is indicated when Zoledronic Acid is administered in conjunction with medicinal products that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration) .
In patients with renal impairment, the systemic exposure to concomitant medicinal products that are primarily excreted via the kidney may increase.

PREGNANCY AND LACTATION

Pregnancy

Zoledronic Acid is contraindicated during pregnancy. Studies in animals with zoledronic acid have shown reproductive toxicological effects including malformations. The potential risk for humans is unknown.

Breast-feeding

Zoledronic Acid is contraindicated during breast-feeding. It is unknown whether zoledronic acid is excreted into human milk.

Women of childbearing potential

Zoledronic Acid is not recommended in women of childbearing potential.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Zoledronic Acid has no or negligible influence on the ability to drive and use machines. Adverse reactions, such as dizziness, may affect the ability to drive or use machines.

UNDESIRABLE EFFECTS

Adverse reactions in Table 1 are listed according to MedDRA system organ class and frequency category.

Table 1

Infections and infestations	*Uncommon*	Influenza, nasopharyngitis
Blood and lymphatic system disorders	*Uncommon*	Anaemia
Immune system disorders	*Not known***	Hypersensitivity reactions including rare cases of bronchoconstriction, urticaria and angioedema, and very rare cases of anaphylactic reaction/shock
Metabolism and nutrition disorders	*Common* *Uncommon* *Rare*	Hypocalcaemia* Decreased appetite Hypophosphataemia
Psychiatric disorders	*Uncommon*	Insomnia
Nervous system disorders	*Common* *Uncommon*	Headache, dizziness Lethargy, paraesthesia, somnolence, tremor, syncope, dysgeusia
Eye disorders	*Common* *Uncommon* *Rare* *Not known***	Ocular hyperaemia Conjunctivitis, eye pain Uveitis, episcleritis, iritis Scleritis and parophthalmia
Ear and labyrinth disorders	*Uncommon*	Vertigo
Cardiac disorders	*Common* *Uncommon*	Atrial fibrillation Palpitations
Vascular disorders	*Uncommon* *Not known***	Hypertension, flushing

		Hypotension (some of the patients had underlying risk factors)
Respiratory, thoracic and mediastinal disorders	*Uncommon*	Cough, dyspnoea
Gastrointestinal disorders	*Common* *Uncommon*	Nausea, vomiting, diarrhoea Dyspepsia, abdominal pain upper, abdominal pain, gastroesophageal reflux disease, constipation, dry mouth, oesophagitis, toothache, gastritis[#]
Skin and subcutaneous tissue disorders	*Uncommon*	Rash, hyperhidrosis, pruritus, erythema
Musculoskeletal and connective tissue disorders	*Common* *Uncommon* *Rare* *Very rare* *Not known*	Myalgia, arthralgia, bone pain, back pain, pain in extremity Neck pain, musculoskeletal stiffness, joint swelling, muscle spasms, musculoskeletal chest pain, musculoskeletal pain, joint stiffness, arthritis, muscular weakness Atypical subtrochanteric and diaphyseal femoral fractures† (bisphosphonate class adverse reaction) Osteonecrosis of the external auditory anal (bisphosphonate class adverse reaction) Osteonecrosis of the jaw
Renal and urinary disorders	*Uncommon* *Not known***	Blood creatinine increased, pollakiuria, proteinuria Renal impairment. Rare cases of renal failure requiring dialysis and rare cases with a fatal outcome have been reported in patients with pre-existing renal dysfunction or other risk factors such as advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy, or dehydration in the post infusion period
General disorders and administration site conditions	*Very common* *Common* *Uncommon* *Not known***	Fever Influenza-like illness, chills, fatigue, asthenia, pain, malaise, infusion site reaction Peripheral oedema, thirst, acute phase reaction, non-cardiac chest pain Dehydration secondary to post-dose symptoms such as fever, vomiting and diarrhoea

Investigations	*Common* *Uncommon*	C-reactive protein increased Blood calcium decreased

[#] Observed in patients taking concomitant glucocorticosteroids.

* Common in Paget's disease only.

** Based on post-marketing reports. Frequency cannot be estimated from available data.

† Identified in post-marketing experience.

OVERDOSE
Patients who have received doses higher than those recommended should be carefully monitored. In the event of overdose leading to clinically significant hypocalcaemia, reversal may be achieved with supplemental oral calcium and/or an intravenous infusion of calcium gluconate.

INCOMPATIBILITIES
This medicinal product must not be allowed to come into contact with any calcium-containing solutions. Zoledronic Acid must not be mixed or given intravenously with any other medicinal products.

SHELF LIFE
Unopened vials: 2 years

After opening:
The solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C. The refrigerated solution should then be equilibrated to room temperature prior to administration.

SPECIAL PRECAUTIONS FOR STORAGE
This medicinal product does not require any special storage conditions.
Before opening:
Store below 30°C

DOSAGE FORM AND PACKAGING
100 ml solution is packed in Type II soda lime silica clear glass vials, capped with Type I bromobutyl rubber stoppers and sealed with aluminum polypropylene flip off seals.

Zoledronic Acid 5mg/100ml solution for infusions is supplied in 1 vial

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