For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only
OR for Specialist Use only

Zoledronic Acid (Injection) Solution for Intravenous Infusion

ROKFOS

COMPOSITION

ROKFOS
Each 100 ml contains:
Zoledronic Acid Monohydrate equivalent to
Zoledronic Acid (anhydrous) ..... 5 mg

DOSAGE FORM
Solution for intravenous infusion
Clear and colourless solution

DESCRIPTION
ROKFOS contains zoledronic acid, which is a bisphosphonate that inhibits osteoclast-mediated bone resorption.

PHARMACOLOGY
Pharmacodynamics
Zoledronic acid belongs to the bisphosphonate class and acts primarily on bone. It is an inhibitor of osteoclast-mediated bone resorption.

The selective action of bisphosphonates on bone is based on their high affinity for mineralized bone. Intravenously administered zoledronic acid rapidly partitions to bone and, as with other bisphosphonates, localizes preferentially at sites of high bone turnover. The main molecular target of zoledronic acid in the osteoclast is the enzyme farnesyl pyrophosphate (FPP) synthase. The relatively long duration of action of zoledronic acid is attributable to its strong binding affinity to bone mineral.

In the osteoporosis treatment trial, the effect of zoledronic acid treatment on markers of bone resorption (serum beta-C-telopeptides [b-CTx]) and bone formation (bone specific alkaline phosphatase [BSAP], serum N-terminal propeptide of type I collagen [P1NP]) was evaluated in patients (subsets ranging from 517 to 1,246 patients) at periodic intervals. Treatment with a 5 mg annual dose of zoledronic acid reduces bone turnover markers to the premenopausal range, with an approximate 55% reduction in b-CTx, a 29% reduction in BSAP, and a 52% reduction in P1NP over 36 months. There was no progressive reduction of bone turnover markers with repeated annual dosing.

Pharmacokinetics
Pharmacokinetic data in patients with osteoporosis and Paget's disease of bone are not available.

Distribution

Single or multiple 5-minute or 15-minute infusions of 2, 4, 8 or 16 mg zoledronic acid were given to 64 patients with cancer and bone metastases. The post-infusion decline of zoledronic acid concentrations in plasma was consistent with a triphasic process showing a rapid decrease from peak concentrations at end-of-infusion to <1% of the C_{max}, 24 hours post-infusion, with population half-lives of $t_{1/2(alpha)}$ at 0.24 hours and $t_{1/2(beta)}$ at 1.87 hours for the early disposition phases of the drug. The terminal elimination phase of zoledronic acid was prolonged, with very low concentrations in plasma between days 2 and 28 post-infusion, and a terminal elimination half-life $t_{1/2(gamma)}$ of 146 hours. The area under the plasma concentration versus time curve (AUC_{0-24h}) of zoledronic acid was dose-proportional from 2–16 mg. The accumulation of zoledronic acid measured over three cycles was low, with mean AUC_{0-24h} ratios for cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36, respectively.

In vitro and *ex vivo* studies showed low affinity of zoledronic acid for the cellular components of human blood. *In vitro* mean zoledronic acid protein binding in human plasma ranged from 28% at 200 ng/mL to 53% at 50 ng/mL.

Metabolism

Zoledronic acid does not inhibit human cytochrome (CY) P450 enzymes *in vitro*. Zoledronic acid does not undergo biotransformation *in vivo*. In animal studies, <3% of the administered intravenous dose was found in the faeces, with the balance either recovered in the urine or taken up by bone, indicating that the drug is eliminated intact via the kidneys. Following an intravenous dose of 20 nCi ^{14}C-zoledronic acid in a patient with cancer and bone metastases, only a single radioactive species with chromatographic properties identical to those of the parent drug was recovered in urine, which suggests that zoledronic acid is not metabolized.

Excretion

In 64 patients with cancer and bone metastases, on average (± S.D.), 39 ± 16% of the administered zoledronic acid dose was recovered in the urine within 24 hours, with only trace amounts of drug found in urine post-day 2. The cumulative percent of drug excreted in the urine over 0–24 hours was independent of dose. The balance of drug not recovered in urine over 0–24 hours, representing drug presumably bound to bone, is slowly released back into the systemic circulation, giving rise to the observed prolonged low plasma concentrations. The 0–24 hour renal clearance of zoledronic acid was 3.7 ± 2.0 L/h.

Zoledronic acid clearance was independent of dose but dependent upon the patient's creatinine clearance. In a study in patients with cancer and bone metastases, increasing the infusion time of a 4 mg dose of zoledronic acid from 5 minutes (n=5) to 15 minutes (n=7) resulted in a 34% decrease in the zoledronic acid concentration at the end of the infusion ([mean ± S.D.] 403 ± 118 ng/mL versus

264 ± 86 ng/mL) and a 10% increase in the total AUC (378 ± 116 ng × h/mL versus 420 ± 218 ng × h/mL). The difference between the AUC means was not statistically significant.

INDICATIONS

- For the treatment of postmenopausal osteoporosis.
- For the treatment of osteoporosis in postmenopausal women and in men who are at increased risk of fracture, including those with recent low trauma hip fracture.
- Prevention of clinical fractures after fracture in men and women.
- Paget's disease of the bone.

Important Limitations of Use

The safety and effectiveness parameters of zoledronic acid for the treatment of osteoporosis are based on clinical data of 3 years duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis. Patients at low-risk for fracture should be considered for drug discontinuation after 3–5 years of use. Patients who discontinue therapy should have their risk for fracture re-evaluated periodically.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

Patients must be appropriately hydrated prior to the administration of ROKFOS. The intravenous infusion should be followed by a 10 mL normal saline flush of the intravenous line.

Administration of acetaminophen following ROKFOS administration may reduce the incidence of acute-phase reaction symptoms.

A 5 mg dose of ROKFOS administered intravenously is recommended for patients with creatinine clearance >35 mL/min.

Zoledronic acid is contraindicated in patients with creatinine clearance <35 mL/min and in those with evidence of acute renal impairment.

There is no safety or efficacy data to support the adjustment of the zoledronic acid dose, based on baseline renal function. Therefore, no dose adjustment is required in patients with creatinine clearance >35 mL/min.

Prevention of Postmenopausal Osteoporosis

The recommended regimen is a single intravenous infusion of 5 mg ROKFOS administered once every 2 years over no less than 15 minutes. Patients must be adequately supplemented with calcium and vitamin D if dietary intake is not

sufficient. Postmenopausal women require an average of 1,200 mg of calcium and 800–1,000 IU of vitamin D daily.

Treatment of Postmenopausal Osteoporosis
The recommended regimen is a single intravenous infusion of 5 mg ROKFOS administered once a year given over no less than 15 minutes. For osteoporosis treatment, and to reduce the risk of hypocalcaemia, patients must be adequately supplemented with calcium and vitamin D if dietary intake is not sufficient. Postmenopausal women require an average of at least 1,200 mg of calcium and 800–1,000 IU of vitamin D daily.

Treatment to Increase Bone Mass in Men with Osteoporosis
The recommended regimen is a single intravenous infusion of 5 mg ROKFOS administered once a year given over no less than 15 minutes. Patients must be adequately supplemented with calcium and vitamin D if dietary intake is not sufficient. An average of at least 1,200 mg of calcium and 800–1,000 IU of vitamin D daily is recommended.

Treatment and Prevention of Glucocorticoid-Induced Osteoporosis
The recommended regimen is a single intravenous infusion of 5 mg ROKFOS administered once a year given over no less than 15 minutes. Patients must be adequately supplemented with calcium and vitamin D if dietary intake is not sufficient. An average of at least 1,200 mg of calcium and 800–1,000 IU of vitamin D daily is recommended.

Treatment of Paget's disease
ROKFOS should be prescribed only by physicians with experience in the treatrnent of Paget's disease of the bone. The recommended regimen is a single intravenous infusion of 5 mg ROKFOS given over no less than 15 minutes.

To reduce the risk of hypocalcaemia, all patients should receive 1,500 mg elemental calcium daily in divided doses (750 mg two times a day, or 500 mg three times a day) and 800 IU vitamin D daily, particularly in the 2 weeks following ROKFOS administration. All patients should be instructed on the importance of calcium and vitamin D supplementation in maintaining serum calcium levels, and on the symptoms of hypocalcaemia.

Re-treatment of Paget's disease
Specific re-treatment data are not available. After a single treatment with zoledronic acid in Paget's disease, an extended remission period is observed in responding patients.

However, re-treatment with zoledronic acid may be considered in patients who have relapsed, based on increases in serum alkaline phosphatase, or in those patients who failed to achieve normalization of their serum alkaline phosphatase, or in those patients with symptoms, as dictated by medical practice.

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

ROKFOS can be infused without regard to meals.

The incidence of post-dose symptoms occurring within the first 3 days after administration of zoledronic acid can be reduced with the administration of paracetamol or ibuprofen shortly following zoledronic acid administration.

Zoledronic acid solution for infusion must not be allowed to come in contact with any calcium-containing solutions, and should be administered as a single intravenous solution through a separate vented infusion line.

CONTRAINDICATIONS

- Hypocalcaemia.
- Zoledronic acid is contraindicated in patients with creatinine clearance <35 ml/min and in those with evidence of acute renal impairment due to an increased risk of renal failure.
- Hypersensitivity to the active substance or any of the excipients: hypersensitivity reactions, including rare cases of urticaria, angio-oedema, and anaphylactic reaction/shock, have been reported.
- Pregnancy and lactation.

WARNINGS AND PRECAUTIONS

General

A single dose of ROKFOS should not exceed 5 mg and the duration of infusion should be no less than 15 minutes.

Hypocalcaemia and Mineral Metabolism

Zoledronic acid may cause hypocalcaemia. Pre-existing hypocalcaemia must be treated by adequate intake of calcium and vitamin D before initiating therapy with zoledronic acid. Pre-existing disturbances of calcium and mineral metabolism (e.g. hypo-parathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of the small intestine) must be effectively treated, and clinical monitoring of calcium and mineral levels is highly recommended for these patients.

Elevated bone turnover is a characteristic of Paget's disease of the 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 zoledronic acid. Hypocalcaemia following zoledronic acid administration is a significant risk in Paget's disease. All patients should be instructed on the importance of calcium and vitamin D supplementation in maintaining serum calcium levels, and on the symptoms of hypocalcaemia.

All osteoporosis patients should be instructed on the importance of calcium and vitamin D supplementation in maintaining serum calcium levels.

Renal Impairment

A single dose of zoledronic acid should not exceed 5 mg and the duration of infusion should be no less than 15 minutes. Zoledronic acid is contraindicated in patients with creatinine clearance <35 mL/min and in those with evidence of acute renal impairment. If history or physical signs suggest dehydration, zoledronic acid therapy should be withheld until normovolaemic status has been achieved. Zoledronic acid should be used with caution in patients with chronic renal impairment. Acute renal impairment, including renal failure, has been observed following the administration of zoledronic acid, especially in patients with pre-existing renal compromise, advanced age, concomitant nephrotoxic medications, concomitant diuretic therapy, or severe dehydration occurring before or after zoledronic acid administration. Acute renal failure has been observed in patients after a single administration. Rare reports of hospitalization and/or dialysis or fatal outcome occurred in patients with underlying moderate-to-severe renal impairment or with any of the risk factors described in this section. Renal impairment may lead to increased exposure of concomitant medications and/or their metabolites that are primarily renally excreted. Creatinine clearance should be calculated based on actual body weight, using the Cockcroft-Gault formula before each zoledronic acid dose. Transient increase in serum creatinine may be greater in patients with impaired renal function; interim monitoring of creatinine clearance should be performed in at-risk patients. Elderly patients and those receiving diuretic therapy are at increased risk of acute renal failure. These patients should have their fluid status assessed and be appropriately hydrated prior to administration of zoledronic acid. Zoledronic acid should be used with caution with other nephrotoxic drugs. Consider monitoring creatinine clearance in patients at-risk for acute renal failure who are taking concomitant medications that are primarily excreted by the kidneys.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported in patients treated with bisphosphonates, including zoledronic acid. Dental surgery may exacerbate the condition. Most cases have been in cancer patients undergoing dental procedures such as tooth extraction. Some cases have occurred in patients with postmenopausal osteoporosis treated with either oral or intravenous bisphosphonates. A routine oral examination should be performed by the prescriber prior to initiation of bisphosphonate treatment. A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with a history of concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene, pre-existing dental disease or infection, anaemia, coagulopathy).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop ONJ 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 ONJ. The clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures
Atypical, low-energy or low-trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates. Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

Musculoskeletal Pain
In postmarketing experience, severe and, occasionally, incapacitating bone, joint and/or muscle pain has been reported in patients taking bisphosphonates, including zoledronic acid.

The time to onset of symptoms varied from one day to several months after starting the drug. Consider withholding future zoledronic acid treatment if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when re-challenged with the same drug or another bisphosphonate.

Laboratory Test Interactions
Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with zoledronic acid have not been performed.

Patients with Asthma
While not observed in clinical trials with zoledronic acid, there have been reports of bronchoconstriction in aspirin-sensitive patients receiving bisphosphonates. Use zoledronic acid with caution in aspirin-sensitive patients.

Pregnancy

ZOLEDRONIC ACID SHOULD NOT BE USED DURING PREGNANCY. Zoledronic acid may cause foetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the foetus.

Women of childbearing potential should be advised to avoid becoming pregnant while on zoledronic acid therapy.

Drug Interactions

The time to onset of symptoms varied from 1 day to several months after starting the drug. Consider withholding future zoledronic acid treatment if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when re-challenged with the same drug or another bisphosphonate.

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. This has not been reported in zoledronic acid clinical trials. Caution should also be exercised when zoledronic acid is used in combination with loop diuretics due to an increased risk of hypocalcaemia. Caution is indicated when zoledronic acid is used with other potentially nephrotoxic drugs such as anti-inflammatory drugs.

Renal impairment has been observed following the administration of zoledronic acid in patients with pre-existing renal compromise or other risk. In patients with renal impairment, the exposure to concomitant medications that are primarily renally excreted (e.g. digoxin) may increase. Consider monitoring serum creatinine in patients at risk for renal impairment who are taking concomitant medications that are primarily excreted by the kidneys.

Zoledronic acid is not systemically metabolized and does not affect human CYP450 enzymes *in vitro*. 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.

Renal Impairment

Zoledronic acid is contraindicated in patients with creatinine clearance <35 mL/min and in those with evidence of acute renal impairment.

There is no safety or efficacy data to support the adjustment of the zoledronic acid dose based on baseline renal function. Therefore, no dosage adjustment is required in patients with a creatinine clearance of >35 mL/min.

Risk of acute renal failure may increase with underlying renal disease and dehydration secondary to fever, sepsis, gastrointestinal losses, diuretic therapy, advanced age, etc.

Hepatic Impairment
Zoledronic acid is not metabolized in the liver. No clinical data are available for the use of zoledronic acid in patients with hepatic impairment.

Pregnancy
Pregnancy Category D
ZOLEDRONIC ACID SHOULD NOT BE USED DURING PREGNANCY. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the foetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving zoledronic acid.

Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone and, hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on foetal risk in humans, bisphosphonates do cause foetal harm in animals, and animal data suggest that uptake of bisphosphonates into foetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of foetal harm (e.g. skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception space, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been established.

Lactation
It is not known whether zoledronic acid is excreted in human milk. Because many drugs are excreted in human milk, and because zoledronic acid binds to bone long-term, zoledronic acid should not be administered to a lactating woman.

Paediatric Use
Zoledronic acid is not indicated for use in children.

The safety and effectiveness of zoledronic acid was studied in a 1-year active controlled trial of 152 paediatric subjects (74 receiving zoledronic acid). The enrolled population was subjects with severe osteogenesis imperfecta, aged 1 to 17 years, 55% male, 84% Caucasian, with a mean lumbar spine bone mineral density (BMD) of 0.431 gm/cm^2, which is 2.7 standard deviations below the mean for age-matched controls (BMD Z-score of –2.7). At 1 year, increases in the BMD were observed in the zoledronic acid treatment group. However, changes in the BMD in individual patients with severe osteogenesis imperfecta did not necessarily correlate with the risk for fracture or the incidence or severity of chronic bone pain.

The adverse events observed with zoledronic acid use in children did not raise any new safety findings beyond those previously seen in adults treated for Paget's disease of the bone and treatment of osteoporosis, including ONJ and renal impairment. However, adverse reactions seen more commonly in paediatric patients included pyrexia (61%), arthralgia (26%), hypocalcaemia (22%), and headache (22%). These reactions, excluding arthralgia, occurred most frequently within 3 days after the first infusion and became less common with repeat dosing. No cases of ONJ or renal impairment were observed in this study. Because of long-term retention in the bone, zoledronic acid should only be used in children if the potential benefit outweighs the potential risk.

Plasma zoledronic acid concentration data was obtained from 10 patients with severe osteogenesis imperfecta (4 in the age group of 3 to 8 years and 6 in the age group of 9 to 17 years) infused with 0.05 mg/kg dose over 30 minutes. Mean C_{max} and $AUC_{(0-last)}$ were 167 ng/mL and 220 ng.h/mL, respectively. The plasma concentration time profile of zoledronic acid in paediatric patients represents a multi-exponential decline, as observed in adult cancer patients at an approximately equivalent mg/kg dose.

Geriatric Use

The combined osteoporosis trials included 4,863 zoledronic acid-treated patients who were at least 65 years old, while 2,101 patients were at least 75 years old. No overall differences in efficacy or safety were observed between patients under 75 years of age with those at least 75 years of age, except that the acute phase reactions occurred less frequently in the older patients.

Of the patients receiving zoledronic acid in the osteoporosis study in men, and glucocorticoid-induced osteoporosis and Paget's disease studies, 83, 116 and 132 patients, respectively, were 65 years of age or over, while 24, 29 and 68 patients, respectively, were at least 75 years of age.

However, because decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

UNDESIRABLE EFFECTS

Acute-Phase Reactions

Zoledronic acid has been associated with the signs and symptoms of acute-phase reaction, influenza-like illness, pyrexia, myalgia, arthralgia, and bone pain.

Symptoms usually occur within the first 3 days following zoledronic acid administration. One or more of these events which were suspected to be related to the drug were reported in 25% of patients in the zoledronic acid-treated group, compared to 8% in the risedronate-treated group. The majority of these symptoms resolved within 4 days of onset.

Injection Site Reactions

Local reactions at the infusion site such as itching, redness, swelling and/or pain have been observed infrequently following the administration of zoledronic acid.

Ocular Adverse Events
Cases of iritis/uveitis/episcleritis have been reported in patients treated with bisphosphonates, although no cases were reported in the Paget's disease clinical studies. Conjunctivitis has been reported in patients treated with zoledronic acid.

ONJ
ONJ has been reported with zoledronic acid.

Gastrointestinal Disorders
Nausea, diarrhoea, constipation, dyspepsia, abdominal discomfort, abdominal distension, abdominal pain and vomiting have been reported.

Renal Dysfunction
Treatment with intravenous bisphosphonates has been associated with renal dysfunction manifested as deterioration in renal function (i.e. increased serum creatinine) and, in rare cases, acute renal failure. Renal dysfunction has been observed following the administration of zoledronic acid, especially in patients with pre-existing renal compromise or additional risk factors (e.g. oncology patients with chemotherapy, concomitant nephrotoxic medications, severe dehydration, etc.), the majority of whom received a 4 mg dose every 3–4 weeks, but it has been observed in patients after a single administration. In clinical trials in Paget's disease there is no evidence of renal deterioration following a single 5 mg, 15-minute infusion.

Bronchoconstriction in Aspirin-Sensitive Asthma Patients
While not observed in clinical trials, there have been previous reports of bronchoconstriction in aspirin-sensitive patients receiving bisphosphonates.

The adverse reactions are summarized in the table below according to the MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and, not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

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 angio-oedema, and very

		rare cases of anaphylactic reaction/shock
Metabolism and nutrition disorders	*Common*	Hypocalcaemia*
	Uncommon	Anorexia, decreased appetite
Psychiatric disorders	*Uncommon*	Insomnia
Nervous system disorders	*Common*	Headache, dizziness, hypoaesthesia
	Uncommon	Lethargy, paraesthesia, somnolence, tremor, syncope, dysgeusia
Eye disorders	*Common*	Ocular hyperaemia
	Uncommon	Conjunctivitis, eye pain
	Rare	Uveitis, episcleritis, iritis
	*Not known***	Scleritis and orbital inflammation
Ear and labyrinth disorders	*Uncommon*	Vertigo
Cardiac disorders	*Common*	Atrial fibrillation
	Uncommon	Palpitations
Vascular disorders	*Uncommon*	Hypertension, flushing
	*Not known***	Hypotension (some of the patients had underlying risk factors)
Respiratory, thoracic and mediastinal disorders	*Uncommon*	Cough, dyspnoea
Gastrointestinal disorders	*Common*	Nausea, vomiting, diarrhoea
	Uncommon	Dyspepsia, upper abdominal pain, abdominal pain, gastro-oesophageal reflux disease, constipation, dry mouth, oesophagitis, toothache, gastritis#
Skin and subcutaneous tissue disorders	*Uncommon*	Rash, hyperhydrosis, pruritus, erythema
Musculoskeletal and	*Common*	Myalgia, arthralgia, bone pain,

connective tissue disorders		back pain, pain in extremity, osteoarthritis, joint swelling, flank pain, pain in jaw
	Uncommon	Neck pain, musculoskeletal stiffness, joint swelling, muscle spasms, shoulder pain, musculoskeletal chest pain, musculoskeletal pain, joint stiffness, arthritis, muscular weakness
	Rare	Atypical subtrochanteric and diaphyseal femoral fractures† (bisphosphonate-class adverse reaction)
	*Not known***	ONJ
Renal and urinary disorders	*Uncommon*	Blood creatinine increased, pollakiuria, proteinuria
	*Not known***	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*	Fever
	Common	Flu-like symptoms, chills, fatigue, asthenia, pain, malaise, infusion site reaction
	Uncommon	Peripheral oedema, thirst, acute phase reaction, non-cardiac chest pain
	*Not known***	Dehydration secondary to post-dose symptoms such as fever, vomiting and diarrhoea

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

Observed in patients taking concomitant glucocorticosteroids.
* Common in Paget's disease only.
** Based on postmarketing reports. Frequency cannot be estimated from available data.
† Identified in postmarketing experience.

Postmarketing Experience
Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions have been identified during post-approval use of zoledronic acid infusion:

Acute Phase Reactions
Fever, headache, flu-like symptoms, nausea, vomiting, diarrhoea, arthralgia, and myalgia. Symptoms may be significant and lead to dehydration.

Acute Renal Failure
Acute renal failure requiring hospitalization and/or dialysis or with a fatal outcome have been rarely reported. Increased serum creatinine was reported in patients with 1) underlying renal disease, 2) dehydration secondary to fever, sepsis, gastrointestinal losses, or diuretic therapy, or 3) other risk factors such as advanced age, or concomitant nephrotoxic drugs in the post-infusion period. Transient rise in serum creatinine can be correctable with intravenous fluids.

Allergic Reactions
Allergic reactions with intravenous zoledronic acid, including anaphylactic reaction/shock, urticaria, angio-oedema and bronchoconstriction, have been reported.

Asthma Exacerbations
Asthma exacerbations have been reported.

Hypocalcaemia
Hypocalcaemia has been reported.

ONJ
ONJ has been reported.

Ocular Adverse Events
Cases of the following events have been reported: conjunctivitis, iritis, iridocyclitis, uveitis, episcleritis, scleritis and orbital inflammation/oedema.

Other
Hypotension in patients with underlying risk factors has been reported.

OVERDOSAGE
There is limited experience of acute overdose with zoledronic acid injection. Patients who have received doses higher than those recommended should be carefully monitored. Overdosage may cause clinically significant renal impairment, hypocalcaemia, hypophosphataemia, and hypomagnesaemia. Clinically relevant reductions in serum levels of calcium, phosphorus and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulphate, respectively.

Single doses of **ROKFOS** should not exceed 5 mg and the duration of the intravenous infusion should be no less than 15 minutes.

INCOMPATIBILITY
Zoledronic acid 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.

STORAGE AND HANDLING INSTRUCTIONS

- Store at 25°C. Excursions permitted to 15–30°C.
- Keep out of the reach of children.
- Do not mix with any calcium-containing solutions.

PACKAGING INFORMATION
ROKFOS is available in a bottle of 100 ml.

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