ZOLEDRONIC ACID HIKMA®

PHARMACODYNAMICS

Zoledronic acid belongs to a new highly potent class of bisphosphonates which act primarily on bone. It is one of the most potent inhibitors of osteoclastic bone resorption known to date. The selective action of bisphosphonates on bone is based on their high affinity for mineralised bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity is still unclear. In long-term animal studies, zoledronic acid inhibits bone resorption without adversely affecting the formation, mineralization or mechanical properties of bone.

In addition to being a very potent inhibitor of bone resorption, zoledronic acid also possesses several anti-tumour properties that could contribute to its overall efficacy in the treatment of metastatic bone disease. The following properties have been demonstrated in preclinical studies:

- In vivo: Inhibition of osteoclastic bone resorption, which alters the bone marrow microenvironment making it less conducive to tumour cell growth, anti-angiogenic activity, anti-pain activity.
- In vito: inhibition of osteoblast proliferation, direct cytostatic and pro-apoptotic activity on tumour cells, synergistic cytostatic effect with other anticancer drugs, anti-adhesion/ invasion activity.

PHARMACOKINETICS

Single and multiple 5- and 15- minute infusions at 2, 4, 8 and 16 mg zoledronic acid in 64 patients with bone metastases yielded the following pharmacokinetic data, which were found to be dose independent.

After initiating the infusion of zoledronic acid, the plasma concentrations of drug rapidly increased, 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 prior to the second infusion of drug on day 28. Intravenously administered zoledronic acid is eliminated via a triphasic process: rapid biphasic disappearance from the systemic circulation, with halt-lives of t1/2 alpha 0.24 and t1/2 beta 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of t1/2 gamma 146 hours.

There was no accumulation of drug in plasma after multiple doses of the drug given every 28 days. Zoledronic acid is not metabolized and is excreted unchanged via the kidney. Over the first 24 hours, 39 ± 16 % ar the administered dose is recovered in the urine, while the remainder is principally bound to bone tissue. From the bone tissue it is released very slowly back into the systemic circulation and eliminated via the kidney. The total body clearance is 5.04 ± 2.5 L/h, independent of dose, and unaffected by gender, age, race, and body weight. Increasing the infusion time from 5 to 15 minutes caused a 30 % decrease in zoledronic acid concentration at the end of the infusion, but had no effect on the area under the plasma concentration versus time curve.

No pharmacokinetic data for zoledronic acid are available in patients with hypercalcaemia or in patients with hepatic Insufficiency. Zoledronic acid does not inhibit human P450 enzymes In Vitro, shows no biotransformation and in animal studies < 3% of the administered dose was recovered in the faeces, suggesting no relevant role of liver function in the pharmacokinetics of zoledronic acid.

The renal clearance of zoledronic acid was significantly positively correlated with creatinine clearance; renal clearance representing 75 ± 33% of the creatinine clearance, which showed a mean of 84 ± 29 mL/min (range 22 to 143 mL/min) in the 64 cancer patients studied. Population analysis showed that for a patient with creatinine clearance of 20 mL/min (severe renal impairment), or 50 mL/min (moderate impairment), the corresponding predicted clearance of zoledronic acid would be 37% or 72%, respectively, of that of a patient showing creatinine clearance at 84 mL/min. Only limited pharmacokinetic data are available in patients with severe renal insufficiency (creatinine clearance < 30 mL/min). Zoledronic acid show; no affinity for the cellular components of blood and plasma protein binding is low (approximately 56 %) and independent on the concentration of zoledronic acid.

INDICATIONS

Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone.

Treatment of hypercalcaemia of malignancy (HCM).

DOSAGE AND ADMINISTRATION

Prevention of skeletal related events in patients with advanced malignancies involving bone

Adults and elderly

The recommended dose in the prevention of skeletal related events in patients with advanced malignancies involving bone is 4 mg zoledronic acid. After reconstitution, the vial must be further diluted with 100 mL 0.9 % w/v sodium chloride or 5 % w/v glucose solution and given as an intravenous infusion lasting no less than 15 minutes every 3 to 4 weeks. Patients should also be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily.

Treatment of HCM

Adults and elderly

The recommended dose in hypercalcaemia (albumin-corrected serum calcium >= 12.0 mg/dL or 3.0 mmol/L) is 4 mg zoledronic acid. After reconstitution, the vial must be further diluted with 100 mL 0.9 % w/v sodium chloride or 5 % w/v glucose solution, given as a single intravenous infusion of no less than 15 minutes. Patients must be maintained well hydrated prior to and following administration of zoledronic acid.

Renal impairment

HCM:

Zoledronic acid treatment in patients with hypercalcaemia of malignancy (HCM) and who have severe renal impairment should be considered only after evaluating the risks and benefit of treatment. In the clinical studies, patients with serum creatinine > 400 micromol/L or > 4.5 mg/dL were excluded. No dose adjustment is necessary in HCM patients with serum creatinine < 400 micromol/L or < 4.5 mg/dL (see section SPECIAL WARNINGS ANO PRECAUTIONS FOR USE).

Prevention of skeletal related events in patients with advanced malignancies involving bone:

When initiating treatment with zoledronic acid in patients with multiple myeloma or metastatic bone lesions from solid tumours, serum creatinine levels and creatinine clearance (CrCl) should be determined. CrCl is calculated from serum creatinine levels using the Cockcroft-Gault formula. Zoledronic acid is not recommended for patients presenting with severe renal impairment prior to initiation of therapy, which is defined for this population as CrCl < 30 mL/min. In clinical trials with zoledronic acid, patients with serum creatinine > 265 micromol/L or > 3.0 mg/dL were excluded.

In patients with bone metastases presenting with mild to moderate renal impairment prior to initiation of therapy, which is defined for this population as CrCl 30 to 60 mL/ min, the following zoledronic acid dose is recommended (see also section SPECIAL WARNINGS AND PRECAUTIONS FOR USE):

Baseline Creatinine Clearance (mL/min)	Zoledronic acid Recommended Dose
> 60	4.0 mg
50-60	3.5 mg*
40-49	3.3 mg*
30-39	10 mg*

*Doses have been calculated assuming target AUC of 0.66 (mg.hr/L) (CrCl=75ml/mm). The reduced doses for patients with renal impairment are expected to achieve the same AUC as that seen in patients with creatinine clearance of 75 mL/min.

Following initiation of therapy, serum creatinine should be measured prior to each dose of zoledronic acid and treatment should be withheld if renal function has deteriorated. In the clinical trials, renal deterioration was defined as follows:

- For patients with normal baseline serum creatinine (< 1.4 mg/dL), an increase of >= 0.5 mg/dL;
- For patients <With an abnormal baseline creatinine (> 1.4 mg/dL), an increase of >= 1.0 mg/dL.

In the clinical studies, zoledronic acid treatment was resumed only when the creatinine level returned to within 10% of the baseline value (see section SPECIAL WARNINGS ANO PRECAUTIONS FOR USE). Zoledronic acid should be resumed at the same dose as that prior to treatment interruption.

Instructions on preparing reduced doses of zoledronic acid

After reconstitution, withdraw an appropriate volume of the liquid concentrate needed, as follows:

4.4 mL	for 3.5 mg dose
4.1 mL	for 3.3 mg dose
3.8 mL	for 3.0 mg dose

The withdrawn amount of liquid concentrate must be further diluted in 100 mL of sterile 0.9% w/v sodium chloride solution or 5% w/v glucose solution. The dose must be given as a single intravenous infusion of no less than 15 minutes.

CONTRAINDICATIONS

Zoledronic acid is contraindicated in pregnancy, in breast-feeding women, patients with clinically significant hypersensitivity to zoledronic acid or other bisphosphonates or any of the excipients in the formulation of zoledronic acid.

WARNINGS AND PRECAUTIONS

General

Patients must be assessed prior to administration of zoledronic acid to assure that they are adequately hydrated. Overhydration should be avoided in patients at risk of cardiac failure. Standard hypercalcaemia-related metabolic parameters, such as serum levels of calcium, phosphate and magnesium as well as serum creatinine should be carefully monitored after initiating zoledronic acid therapy. If hypocalcaemia, hypophosphataemia, or hypomagnesaemia occur, short-term supplemental therapy may be necessary. Untreated hypercalcaemia patients generally have some degree of renal function impairment, therefore careful renal function monitoring should be considered.

Zoledronic acid contains the same active ingredient as found in Aclasta (zoledronic acid). Patients being treated with zoledronic acid should not be treated with Aclasta concomitantly. The safety and efficacy of zoledronic acid in paediatric patients have not been established.

Renal insufficiency

Patients with HCM with evidence of deterioration in renal function should be appropriately evaluated with consideration given as to whether the potential benefit of continued treatment With zoledronic acid outweighs the possible risk.

The decision to treat patients with bone metastases for the prevention of skeletal related events should consider that the onset of treatment effect is 2 to 3 months. Bisphosphonates have been associated with reports of renal dysfunction.

Factors that may increase the potential for deterioration in renal function include dehydration, preexisting renal impairment, multiple cycles of zoledronic acid or other bisphosphonates as well as use of nephrotoxic drugs or using a shorter infusion time than currently recommended. While the risk is reduced with a dose of zoledronic acid 4 mg administered over no less than 15 minutes, deterioration in renal function may still occur. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of zoledronic acid. Increases in serum creatinine also occur in some patients with chronic administration of zoledronic acid at recommended doses for prevention of skeletal related events, although less frequently.

Patients should have their serum creatinine levels assessed prior to each dose of zoledronic acid. Upon initiation of treatment in patients with bone metastases with mild to moderate renal impairment, lower doses of zoledronic acid are recommended. In patients who show evidence of renal deterioration during treatment, zoledronic acid should only be resumed when creatinine level returns to within 10% of baseline value (see section DOSAGE AND ADMINISTRATION).

In view of the potential impact of bisphosphonates, including zoledronic acid, on renal function, the lack of extensive clinical safety data in patients with severe renal impairment (in clinical trials defined as serum creatinine >= 400 micromol/L or >= 4.5 mg/dL for patients with HCM and >= 265 micromol/L or > 3.0 mg/dL for patients with cancer and bone metastases, respectively) at baseline and only limited pharmacokinetic data in patients with severe renal impairment at baseline (creatinine clearance < 30 ml/min), the use of zoledronic acid is not recommended in patients With severe renal impairment.

Hepatic insufficiency

As only limited clinical data are available in patients with severe hepatic insufficiency, no specific recommendations can tie given for this patient population.

Osteonecrosis of the jaw

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, corticosteroids, poor oral hygiene).

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. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit /risk assessment.

Musculoskeletal pain

In post-marketing experience, severe and occasionally incapacitating bone, Joint, and/or muscle pain have been reported in patients taking bisphosphonates. However, such reports have been infrequent. This category of drugs includes zoledronic acid. The time to onset of symptoms varied from one day to several months after starting treatment. Most patients had relief of symptoms after stopping treatment. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

DRUG INTERACTIONS

In clinical studies, zoledronic acid has been administered concomitantly with commonly used anticancer agents, diuretics, antibiotics and analgesics without clinically apparent interactions occurring. Zoledronic acid shows no appreciable binding to plasma proteins and does not inhibit human P450 enzymes in vitro(see section PHARMACOKINETICS), but no formal clinical interaction studies have been performed. Caution is advised when bisphosphonates like zoledronic acid are administered with aminoglycosides, since both agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required. Caution is indicated when zoledronic acid is used with other potentially nephrotoxic drugs. Attention should also be paid to the possibility of hypomagnesaemia developing during treatment.

In multiple myeloma patients, the risk of renal dysfunction may be increased when intravenous bisphosphonates like zoledronic acid are used in combination with thalidomide.

Pregnancy and lactation

In animal reproduction studies zoledronic acid was administered subcutaneously to rats and rabbits. It was found to be teratogenic at doses >= 0.2 mg/kg bodyweight in rats. In rabbits, there was no teratogenicity or foetotoxicity but maternotoxicity was found. Zoledronic acid should not be used during pregnancy.

It is not known wither zoledronic acid is excreted into human milk. Zoledronic acid should not be used by breast-feeding women (see section CONTRAINDICATIONS).

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

SIDE EFFECTS

Frequencies of adverse reactions for zoledronic acid 4 mg are mainly based on data collected from chronic treatment Adverse reactions to zoledronic acid are usually mild and transient and similar to those reported for other bisphosphonates. Those reactions can be expected to occur in approximately one third of patients either for zoledronic acid or for pamidronate 90 mg. Intravenous administrations has been most commonly associated with a flu-like syndrome in about 9 % of patients including bone pain, fever, fatigue and rigors. Occasionally cases of arthralgia and myalgia in approximately 3 % of patients have been reported.

Frequently, the reduction in renal calcium excretion is accompanied by a fall in serum phosphate levels in approximately 20 % of patients, which is asymptomatic not requiring treatment. The serum calcium may fall to asymptomatic hypocalcaemic levels in approximately 3 % of patients.

Gastrointestinal reactions, such as nausea (5.8 %), and vomiting (2.6 %) have been reported following intravenous infusion of zoledronic acid.

Occasionally local reactions at the infusion site such as redness or swelling and/or pain were also observed in less than 1% of the patients.

Anorexia was reported in 1.5% of patients treated with zoledronic acid 4 mg.

Few cases of rash or pruritus, have been observed (below 1%). As with other bisphosphonates, cases of conjunctivitis in approximately 1% have been reported.

There have been some reports of impaired renal function (2.3 %); however, other risk factors in this ill patient population may have contributed as well.

Based on pooled analysis of placebo controlled studies, severe anemia (Hb < 8.0 g/dL) was reported in 5.2% of patients receiving zoledronic acid 4 mg versus 4.2% on placebo. The following adverse drug reactions, listed in the following table, have been accumulated from clinical studies following predominantly chronic treatment with zoledronic acid:

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention:

Very common (>=1/10), common (>=1/100, <1/10), uncommon (>=1/1000, < 1/100), rare (= 1/10,000,< 1/1000), very rare (<1/10,000), including isolated reports.

Blood and lymphatic system disorders	
Common	Anemia
Uncommon	Thrombocytopenia, leucopenia
Rare	Pancytopenia
Nervous system disorders	
Common	Headache
Uncommon	Dizziness, paraesthesia, taste disturbance, nypoaesthesia, hyperaesthasia, tremor
Psychiatric disorders	
Uncommon	Anxiety, sleep disturbance
Rare	Confusion
Eye disorders	
Common	Conjunctivitis
Uncommon	Blurred Vision
Very rare	Uveitis, episcleritis
Gastrointestinal disorders	
Common	Nausea, vomiting, anorexia
Uncommon	Diarrhea, constipation, abdominal pain, dyspepsia, stomatitis, dry mouth
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, cough
Skin and subcutaneous tissue disorders	
Uncommon	Pruritus, rash (including erythematous and macular rash), increased sweating
Musculoskeletal, connective tissue and bone disorders	
Common	Bone pain, myalgia, arthralgia, generalized pain
Uncommon	Muscle cramps
Cardiovascular disorders	
Uncommon	Hypertension, hypotension
Rare	Bradycardia
Renal and urinary disorders	
Common	Renal impairment
Uncommon	Acute renal failure, haematuria, Proteinuria
Immune system disorders	
Uncommon	Hypersensitivity reaction
Rare	Angioneurotic oedema
General disorders and administration site conditions	
Common	Fever, flu like syndrome (including: fatigue, rigors, malaise and flushing)
Uncommon	Asthenia, peripheral oedema, injection site reactions (including: pain, irritation, swelling, induration), chest pain, weight increase
Laboratory abnormalities	
Very common	Hypophosphataemia
Common	Blood creatinine and blood urea increased, hypocalcaemia
Uncommon	Hypomagnesaemia, hypokalaemia
Rare	Hyperkalaemia, hypernatraemia

While not observed with zoledronic acid, administration of other bisphosphonates has been associated with bronchoconstriction in acetylsalicylic acid-sensitive asthmatic patients. Post-marketing experience: Cases of osteonecrosis (primarily of the jaws) have been reported predominantly in cancer patients treated with bisphosphonates, including zoledronic acid (uncommon). Many of these patients had signs of local infection including osteomyelitis, and the majority of the reports refer to cancer patients following tooth extractions or other dental surgeries. Osteonecrosis of the jaws has multiple well documented risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g. Anemia, coagulopathies, infection, pre-existing oral disease). Although causality has not been determined, it is prudent to avoid dental surgery as recovery may be prolonged (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE). In very rare cases, the following events have been reported: hypotension leading to syncope or circulatory collapse, primarily in patients with underlying risk factors, atrial fibrillation, somnolence, bronchoconstriction.

OVERDOSAGE

Clinical experience with acute overdosage of zoledronic acid is limited. Patients who have received doses higher than those recommended should be carefully monitored, since renal function impairment (including renal failure) and serum electrolyte (including calcium, phosphorus and magnesium) abnormalities have been observed. In the event of hypocalcaemia, calcium gluconate infusions should be administered as clinically indicated.

PRECLINICAL SAFETY DATA

Acute toxicity:

The highest non-lethal single intravenous dose was 10 mg/kg bodyweight in mice and 0.6 mg/kg in rats.

Sub-chronic and chronic toxicity:

Zoledronic acid was well tolerated when administered subcutaneously to rats and intravenously to dogs at doses up to 0.02 mg/kg daily for 4 weeks. Administration of 0.001 mg/kg/day subcutaneously in rats and 0.005 mg/kg/day intravenously In dogs for up to 52 weeks was also well tolerated.

Reproduction toxicity:

Zoledronic acid was teratogenic in the rat at subcutaneous doses >= 0.2 mg/kg. Although no teratogenicity or foetotoxicity was observed in the rabbit, maternal toxicity was found.

Mutagenicity and carcinogenic potential:

Zoledronic acid was not mutagenic in the mutagenicity tests performed and carcinogenicity testing did not provide any evidence of carcinogenic potential.

Local tolerance:

Local tolerance testing in rabbits showed that intravenous administration was well tolerated.

INCOMPATIBILITIES

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

To avoid potential incompatibilities, reconstituted zoledronic acid is to be diluted with 0.9 % w/v sodium chloride solution or 1d: 5 % w/v glucose solution.

Reconstituted zoledronic acid must not be mixed with calcium-containing solutions such as Ringer's solution.

INFORMATION FOR THE HEALTHCARE PROFESSIONALS

How to prepare and administer zoledronic acid

- To prepare an infusion solution containing 4 mg zoledronic acid, further dilute the zoledronic acid lyophilized powder with 100 mL of calcium-free infusion solution. If a lower dose of zoledronic acid is required, first withdraw the appropriate volume (see table below) and dilute it further with 100 mL of infusion solution. To avoid potential incompatibilities, the infusion solution used for dilution must be either 0.9% w/v sodium chloride or 5% w/v glucose solution.

Do not mix zoledronic acid concentrate with calcium-containing solutions such as Ringer's solution.

Instructions on preparing reduced doses of zoledronic acid

After reconstitution, withdraw an appropriate volume of the liquid concentrate needed, as follows:

4.4 mL	for 3.5 mg dose
4.1 mL	for 3.3 mg dose
3.8 mL	for 3.0 mg dose

- After preparation, zoledronic acid infusion solution should preferably be used immediately. If the solution is not used immediately, storage prior to use is the responsibility of the care provider and should be in a refrigerator at 2-8°C up right position. Allow the refrigerated solution to reach room temperature before administration.
- The total time between dilution, storage in the refrigerator and end of administration must not exceed 24 hours.
- The solution containing zoledronic acid is given as a single intravenous infusion of no less than 15 minutes. The hydration status of patients must be assessed prior to and following administration of zoledronic acid to assure that they are adequately hydrated.
- Studies with glass bottles, several types of Infusion bags and infusion lines made from polyvinylchloride, polyethylene and polypropylene (prefilled with 0.9% w/v sodium chloride solution or 5% w/v glucose solution) showed no incompatibility with zoledronic acid.
- Since no data are available on the compatibility of zoledronic acid with other intravenously administered substances, zoledronic acid must not be mixed with other medications/ substances and should always be given through a separate infusion line.

STORAGE

Store below 30°C.

RECONSTITUTION

Add 5 ml of sterile water for injection. The resultant zoledronic acid solution is stable for 24 hours at 2-8°C after further dilution in 100 mL physiological saline or 5 % w/v glucose solution.

After aseptic dilution, it is preferable to use the diluted product immediately. If not used immediately, the duration and conditions of storage prior to use are the care provider's responsibility. The total time between dilution, storage in a refrigerator at 2 to 8°C and end of administration must not exceed 24 hours.

INSTRUCTIONS FOR USE AND HANDLING

Zoledronic acid 4 mg is for intravenous use only. After reconstitution and prior to administration, 5.0 mL concentrate from one vial or the volume of the concentrate from one vial or the volume of concentrate withdrawn as required must be further diluted with 100 mL of calcium-free infusion solution (0.9 % w/v sodium chloride solution or 5 % w/v glucose solution). If refrigerated, the solution must be allowed to reach room a temperature before administration. See also section DOSAGE AND ADMINISTRATION.

PRESENTATION

Vials:

Zoledronic Acid Hikma: Zoledronic acid (as monohydrate) 4 mg

Excipients: Mannitol, Sodium citrate.

THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription strictly, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

HIKMA Pharmaceuticals, Amman - Jordan

Keep medicament out of the reach of children

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