Incompatibilities:
Studies with glass bottles, as well as several types of infusion bags and infusion lines made from polyvinylchloride, polyethylene and (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, Zoledronic acid reconstituted solution is to be diluted with 0.9% w/v sodium chloride solution or 5% w/v glucose solution. Zoledronic acid reconstituted solution must not be mixed with calcium containing solutions such as Ringer's solution.

Special Precaution for Storage:

Storage : Store at a temperature not exceeding 30°C.

Instructions for use and handling

Note: Zoledronic acid Injection should be kept out of the reach of children.

Zoledronic acid 4 mg powder for solution for infusion is for intravenous use only. The powder must first be reconstituted in the vial with 5 ml of Sterile water for Injection. Dissolution must be complete before the solution is withdrawn. The reconstituted solution should is then 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 temperature before administration.

If an 8 mg dose is required (re-treatment), two vials are each to be reconstituted with 5 ml water for injection a described above and the resulting 10 ml reconstituted solution further diluted with 100 ml 0.9% w/v sodium chloride solution or 5%w/v glucose solution.

Do not mix zoledronic acid reconstituted solution with calcium containing solution such as ringer's solution.

The 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°C- 8°C. Allow the refrigerated solution to reach room temperature before administration.

The total time between reconstitution, dilution , storage in the refrigerator and end of administration must not exceed 24 hours.

The solution containing Zoledronic acid is given as a single 15 - minute intravenous infusion.

The hydration status of patients must be assessed prior to administration of zoledronic acid to assure that they are adequately hydrated.

Since no data is 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.

Presentation :

ZOLPROSS 4: Each single dose vial contains 4mg Zoledronic Acid anhydrous as a sterile lyophilized powder individually packed in a carton along with pack insert.

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For the use of Registered Medical Practitioner or a Hospital or a Laboratory only

℞ Zoledronic Acid Injection I.P. 4mg

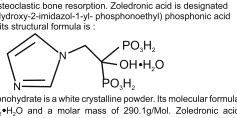
ZOLPROSIS 4
AMERICAN
Injection

Composition :
Each vial contains:

Zoledronic Acid I.P.		
equivalent to Zoledronic Acid Anhydrous		4 mg
Mannitol	I.P.	220 mg
Sodium Citrate	I.P.	24 mg

(As sterile freeze-dried powder for reconstitution)

DESCRIPTION : Zolprosis 4 Contains Zoledronic acid, a bisphosphonic acid which is an inhibitor of osteoclastic bone resorption. Zoledronic acid is designated chemically as (1-Hydroxy-2-imidazol-1-yl- phosphonoethyl) phosphonic acid monohydrate and its structural formula is :



Zoledronic acid monohydrate is a white crystalline powder. Its molecular formula is $C_5H_{10}N_2O_7P_2 \bullet H_2O$ and a molar mass of 290.1g/Mol. Zoledronic acid monohydrate is highly soluble in 0.1 M sodium hydroxide solution, sparingly soluble in water and 0.1 N hydrochloric acid, and practically insoluble in organic solvents. The pH of a 0.7% solution of Zoledronic acid in water is approximately 2.

Clinical Particulars :
Therapeutic Indications
Treatment of hypercalcaemia of malignancy (HCM).

Posology and method of administration
Adults and elderly:
The recommended dose in hypercalcaemia (albumin-corrected serum calcium > 121.0 mg/dl of 3.0 mmol/l) is 4 mg reconstituted and further diluted zoledronic acid solution for infusion (diluted with 100 ml 0.9% w/v sodium chloride or 5% w/v glucose solution), given as a single 15 minute intravenous infusion. The hydration status of patients must be assessed prior to administration of zoledronic acid to assure that patients are adequately hydrated.
Pretreatment : Patients who show complete response (normalization of serum calcium≥ 2.7 mmol/l) and relapse or who are refractory to initial treatment may be retreated with Zoledronic acid 8 mg given as a single 15-minutes intravenous infusion, However, at least one week must elapse before pretreatment to allow for a full response to the initial dose. In clinical studies 69 such patients received pretreatment with Zoledronic acid 8 mg.
The solution for this infusion is prepared by reconstituting two vials of Zoledronic acid, combining them and then further diluting with 100 ml 0.9% w/v sodium chloride or 5% w/v glucose solution. The response rate observed in these retreated patients was 52%. The median time to relapse is 30 days with a dose of 4 mg and 40 days with a dose 8 mg zoledronic acid.
Renal Impairment : Studies of Zoledronic acid in the treatment of hypercalcaemia included patients with serum creatine <400 umol/l or <4.5 mg/dl. In Patients requiring repeated administration of Zoledronic acid, serum creatinine should be measured prior to each dose (see * Special warning and special precautions for use*).

CONTRAINDICATIONS:
Zoledronic acid powder for solution for infusion is contraindicated in patients with clinically significant hypersensitivity to Zoledronic acid, other bisphosphonates or any of the excipients in the formulation of Zoledronic acid.
Special warning and special precautions for use 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.
Bisphosphonates have been associated with reports of renal dysfunction. In view of possible serum creatinine level elevations and the lack of data in patients with severe renal impairment (serum creatinine 400 umol/l or 4.5 mg/dl), the use of zoledronic acid cannot be recommended in these patients unless the benefits outweight the risks.
In any patient requiring repeated administration of Zoledronic acid, serum creatinine should be evaluated prior to each dose. Patients with evidence of renal function deterioration should be appropriately evaluated and consideration should be given as to whether the potential benefit outweighs the possible risk.
As only limited clinical data are available in patients with severe hepatic insufficiency, no specific recommendations can be given for this patient population.

The safety and efficacy of Zoledronic acid in pediatric patients have not been established.
Interaction with other medicinal production and other forms of interaction
In clinical studies, Zoledronic acid has been administered concomitantly with commonly used anti-cancer agents, diuretics, antibiotics and analgesics without clinically apparent interactions occurring. Zoledronic acid shows no appreciable binding to plasma proteins and does not inhibit human P 450 enzymes in vitro but no formal clinical interaction studies have been performed. Caution is advised when bisphonates are administered with amino glycosides, since both agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required. Attention should also be paid to the possibility of hypomagnesemia developing during treatment.
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 body weight in rats. In rabbits, there was no teratogenicity or fetotoxicity but maternotoxicity was found. In the absence of adequate available experience in human pregnancy, Zoledronic acid should not be used during pregnancy unless the benefits to the mother outweigh the risks to the foetus.
It is not known whether Zoledronic acid is excreted into human milk. Zoledronic acid should not be used by breast-feeding women. However, not only are bisphosphonates generally poorly absorbed from the gastrointestinal tract but also any bisphosphonates in milk would be excreted in a bisphosphonate -calcium complex, which is generally thought to be un-absorbable.
Effect on ability to drive and use machines.
No studies on the effects on the ability to drive and use machines have been performed.
Undesirable effects.
Adverse reactions to Zoledronic acid are usually mild and transient and similar to those reported for other bisphosphonates. Intravenous administration has been most commonly associated with a rise in body temperature. Occasionally , a flu-like syndrome consisting of fever, chills and bone and /or muscle ache was reported. In most case no specific treatment is required and the symptoms subside after a couple of hours /days.
Frequently, the reduction in renal calcium excretion in accompanied by a fall in serum phosphate levels not requiring treatment. The serum calcium may fall to asymptomatic hypocalcaemic levels.
Occasionally gastrointestinal reaction, such as nausea and vomiting have been reported following intravenous infusion of Zoledronic acid. Local reactions at the infusion site such as redness or swelling were also observed.
Some cases of rash, pruritus and chest pain have been observed. As with other bisphosphonates, isolated cases of conjunctivitis and hypomagnesaemia have been reported.
In clinical trials performed in patients with hypercalcaemia of malignancy (HCM), the overall safety profile amongst all treatment groups was similar in types and severity.
Grade 3 (NCI Common Toxicity Criteria {CTC}) elevations of serum creatinine were seen in 2.3%, 3.1% and 3.0% of patients receiving Zoledronic acid 4 mg, Zoledronic acid 8 mg and pamidronate 90 mg, respectively, as expected in this disease state and with this class of compounds. There have been some reports of impaired renal function; however, a casual relationslhip has not been established.
While not observed with Zoledronic acid, administration of other bisphosphonates has been associated with broncho constriction in acetylsalicylic acid-sensitive asthmatic paitients.

Overdose
There is no experience of acute intoxication with Zoledronic acid. Patients who have received doses higher than those recommended should be carefully monitored. In the event of clinically significant hypocalcaemia, reversal may be achieved with an infusion of calcium gluconate.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Zoledronic acid belongs to a new highly potent class of bisphosphonates, which act specifically 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 mineralized bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity is still unclear. In long term animals studies, Zoledronic acid inhibits bone resorption without adversely affecting the formation, mineralisation or mechanical properties of bone.

In addition to inhibiting osteoclastic bone resorption, Zoledronic acid exerts direct anti-tumour effects on cultured human myeloma and breast cancer cells, inhibiting proliferation and inducing apoptosis. It also inhibits human endothelial cell proliferation in vitro and is anti-angiogenic in animals. Moreover, the observation that Zoledronic acid reduces the invasion of human breast cancer cells through extracellular matrix in vitro indicated that it may have anti-metastatic properties.

Pharmacokinetic properties

Single 5 and 15 minutes infusions of 2,4,8 and 16 mg Zoledronic acid in 32 patients with bone metastases yielded the following pharmacokinetic data, which were found to be dose independent.
Intravenously administered Zoledronic acid is eliminated via a triphasic process: rapid biphasic disappearance from the systemic circulation, with half-lives of t1/2 a 0.23 and t1/2 b 1.75 hours followed by a long elimination phase with a terminal elimination half-life of t1/2 y 167 hours. Zoledronic acid is not metabolised and is excreted unchanged via the kidney. Over the first 24 hours, 44± 18 % of the administered dose is recovered in the urine, while the remainder is principally bound to bone tissue. From the bone tissue it is release slowly back into the systemic circulation and eliminated via the kidney. The total body clearance is 5.6 ± 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 or severe renal 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.
Zoledronic acid shows no affinity for the cellular components of blood and plasma protein binding is low (approximately 22%) and independent of the concentration of zoledronic acid.
Preclinical safety data
Sub-acute Toxicity Studies:
The studies established that Zolprosis 4 (Zolderonic acid Injection) has not produced any significant changes in physical, physiological, haematological, biochemical and histopathological parameters at three different dose levels upon intravenous administration in rats and mice.
Reproduction Toxicity: Zoledronic acid was teratogenic in the rat at subcutaneous doses ≥0.2 mg/Kg. Although no teratogenicity or fetotoxicity 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.

PHARMACEUTICAL PARTICULARS
List of Excipients
Zoledronic acid vial: Mannitol, sodium citrate

ZOLPROSIS 4
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