1. Name of the finished pharmaceutical product

INN Name: Zoledronic Acid for Injection 4mg/Vial

Trade Name: ZOLDRO

Strength: 4mg/Vial

Pharmaceutical form: Injection

2. Qualitative and quantitative composition

Each mL contains Zoledronic acid monohydrate equivalent to 4 mg of Zoledronic acid, Mannitol Ph. Eur, Sodium Citrate Dihydrate Ph. Eur, and Water for Injection Ph. Eur.

3. Pharmaceutical form

Dosage form: Injection

Description:

A white to off-white lyophilized cake in a 12 ml clear, Type I tubular glass vial with 20 mm neck with grey butyl rubber stopper with flip off seal (20 mm).

4. Clinical particulars

4.1 Therapeutic indications

Hypercalcemia of Malignancy: Zoledronic Acid Injection is indicated for the treatment of hypercalcemia of malignancy following adequate saline rehydration. Vigorous saline hydration, an integral part of hypercalcemia therapy, should be initiated. Promptly and an attempt should be made to restore the urine output to about 2 L/day throughout treatment.

The safety and efficacy of Zoledronic acid in the treatment of hypercalcemia associated with hyperparathyroidism or with other non -tumor-related conditions have not been established.

Infection: Non-specific infection

Laboratory Abnormalities: Hypocalcemia

Metabolic and Nutritional: Dehydration

Musculoskeletal: Arthralgia's

Nervous System: Headache, somnolence

Respiratory System: Pleural effusion

Adverse events are listed regardless of presumed causality to study drug. Among the less frequently occurring adverse events (<15% of patients), rigors, hypokalemia, influenza like illness and hypocalcemia showed a trend for more events with biphosphonate administration compared to placebo group.

Less common adverse events reported more often with Zoledronic acid 4mg than pamidronate included decreased weight, which was reported in 13.0% of patients in the Zoledronic acid 4 mg compared with 7.1% in the pamidronate group. The incidence of decreased weight, however, was similar for the placebo group (12.5%) and Zoledronic acid. Decreased appetite was reported in slightly to patients in the Zoledronic add 4 mg (10.08%) compared with the pamidronate (7.3%) and placebo (8.6%) groups, but the clinical significance of these small difference are not clear

Single doses of Zoledronic acid should not exceed 4 mg and the duration of the intravenous infusion should be no less than 15 minutes.

4.2 Posology and method of administration

Hypercalcemia of Malignancy

The recommended dose of Zoledronic acid in hypercalcemia (albumin corrected serum calcium =12 mg/day) is 4 mg. the 4 mg is given as a single dose i.v infusion over 15 minutes. Patients should be adequately rehydrated prior to administration of Zoledronic acid. Retreatment with Zoledronic acid 4 mg may be considered if serum calcium does not return to normal or remain normal after initial treatment. It is recommended that a minimum of 7 days elapse before retreatment to allow for full response to the initial dose.

Preparation of Solution

Zoledronic acid lyophilized powder for infusion is reconstituted by adding 5mL of sterile water for Injection to each vial. The resulting concentration allows for withdrawal. The content of the reconstituted vials are· withdrawn and further diluted in 100mL of sterile 0.9% sodium chloride or 5% Dextrose injection. Do not store undiluted concentrate in a syringe, to avoid inadvertent injection. The dose must be given as a single intravenous solution infusion over not less than 15 minutes.

If not used immediately after dilution with infusion media, for microbiological integrity, the solution should be refrigerated at $2^{o}C$-$8^{o}C$ ($36^{o}F$-46°F).

Zoledronic acid must not be mixed with calcium containing infusion solutions, such as Lactated Ringer's solution, and should administered as a single intravenous solution in a line separate from all other drugs.

4.3 Contraindications

Zoledronic acid for injection is contraindicated in patients with clinically significant hypersensitivity to Zoledronic acid or other bisphosphonates, or any of the excipients in the formulation of Zoledronic Acid injection.

4.4 Special warnings and precautions for use

WARNINGS

Included as part of the precautions section.

PRECAUTIONS

Drugs with Same Active Ingredient or In the Same Drug Class

Zoledronic Acid Injection contains the same active ingredient as found in Zoledronic acid). Patients being treated with Zoledronic Acid Injection should not be treated with Zoledronic Acid Injection or other bisphosphonates.

Hydration and Electrolyte Monitoring

Patients with hypercalcemia of malignancy must be adequately rehydrated prior to administration of Zoledronic Acid Injection Loop diuretics should not be used until the patient is adequately rehydrated and should be used with caution in combination with Zoledronic Acid Injection in order to avoid hypocalcemia. Zoledronic Acid Injection should be used with caution with other nephrotoxic drugs.

Standard hypercalcemia-related metabolic parameters, such as serum levels of calcium, phosphate, and magnesium, as well as serum creatinine, should be carefully monitored following initiation of therapy with Zoledronic Acid Injection. If hypocalcemia, hypophosphatemia, or hypomagnesemia occur, short-term supplemental therapy may be necessary.

Renal Impairment

Zoledronic Acid Injection is excreted intact primarily via the kidney, and the risk of adverse reactions, in particular renal adverse reactions, may be greater in patients with impaired renal function. Safety and pharmacokinetic data are limited in patients with severe renal impairment and the risk of renal deterioration is increased. Preexisting renal

insufficiency and multiple cycles of Zoledronic Acid Injection and other bisphosphonates are risk factors for subsequent renal deterioration with Zoledronic Acid Injection Factors predisposing to renal deterioration, such as dehydration or the use of other nephrotoxic drugs, should be identified and managed, if possible.

Zoledronic Acid Injection treatment in patients with hypercalcemia of malignancy with severe renal impairment should be considered only after evaluating the risks and benefits of treatment In the clinical studies, patients with serum creatinine greater than 400 µ mol/L or greater than 4.5 mg/dL were excluded.

Zoledronic Acid Injection treatment is not recommended in patients with bone metastases with severe renal impairment. In the clinical studies, patients with serum creatinine greater than 265 µ mol/L or greater than 3.0 mg/dL were excluded and there were only 8 of 564 patients treated with Zoledronic Acid Injection 4 mg by 15-minute infusion with a baseline creatinine greater than 2 mg/dL. Limited pharmacokinetic data exists in patients with creatinine clearance less than 30 mL/min.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported predominantly in cancer patients treated with intravenous bisphosphonates, including Zoledronic Acid Injection. Many of these patients were also receiving chemotherapy and corticosteroids which may be risk factors for ONJ. The risk of ONJ may increase with duration of exposure to bisphosphonates.

Post-marketing experience and the literature suggest a greater frequency of reports of ONJ based on tumor type (advanced breast cancer, multiple myeloma), and dental status (dental extraction, periodontal disease, local trauma including poorly fitting dentures). Many reports of ONJ involved patients with signs of local infection including osteomyelitis.

Cancer patients should maintain good oral hygiene and should have a dental examination with preventive dentistry prior to treatment with bisphosphonates.

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. 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 has been reported in patients taking bisphosphonates, including Zoledronic Acid Injection. The time to onset of symptoms varied from one day to several months after starting the drug. Discontinue use if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical sub-trochanteric and diaphyseal femoral fractures have been reported in patients receiving bisphosphonate therapy, including Zoledronic Acid Injection. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to just above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. These fractures occur after minimal or no trauma. Patients may experience thigh or groin pain weeks to months before presenting with 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. A number of case reports noted that patients were also receiving treatment with glucocorticoids (such as prednisone or dexamethasone) at the time of fracture. Causality with bisphosphonate therapy has not been established.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain in the absence of trauma should be suspected of having an atypical fracture and should be evaluated. Discontinuation of Zoledronic Acid Injection therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment. It is unknown whether the risk of atypical femur fracture continues after stopping therapy.

Patients with Asthma

While not observed in clinical trials with Zoledronic Acid Injection, there have been reports of bronchoconstriction in aspirin-sensitive patients receiving bisphosphonates.

Hepatic Impairment

Only limited clinical data are available for use of Zoledronic Acid Injection to treat hypercalcemia of malignancy in patients with hepatic insufficiency, and these data are not

adequate to provide guidance on dosage selection or how to safely use Zoledronic Acid Injection in these patients.

Use in Pregnancy

Bisphosphonates, such as Zoledronic Acid Injection, are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. There may be a risk of fetal harm (e.g., skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy.

Zoledronic Acid Injection may cause fetal harm when administered to a pregnant woman. In reproductive studies in pregnant rats, subcutaneous doses equivalent to 2.4 or 4.8 times the human systemic exposure resulted in pre-and post-implantation losses, decreases in viable fetuses and fetal skeletal, visceral, and external malformations. There are no adequate and well controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Hypocalcemia

Hypocalcemia has been reported in patients treated with Zoledronic Acid Injection. Cardiac arrhythmias and neurologic adverse events (seizures, tetany, and numbness) have been reported secondary to cases of severe hypocalcemia. In some instances, hypocalcemia may be life-threatening. Caution is advised when Zoledronic Acid Injection is administered with drugs known to cause hypocalcemia, as severe hypocalcemia may develop. Serum calcium should be measured and hypocalcemia must be corrected before initiating Zoledronic Acid Injection. Adequately supplement patients with calcium and vitamin D.

Nonclinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Mice were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. There was an increased incidence of Harderian gland adenomas in males and females in all treatment groups (at doses ≥ 0.002 times a human intravenous dose of 4 mg, based on a comparison of relative body surface areas). Rats were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. No increased incidence of tumors was observed (at doses ≤ 0.2 times the human intravenous dose of 4 mg, based on a comparison of relative body surface areas).

Zoledronic acid was not genotoxic in the Ames bacterial mutagenicity assay, in the Chinese hamster ovary cell assay, or in the Chinese hamster gene mutation assay, with or without metabolic activation. Zoledronic acid was not genotoxic in the *in vivo* rat micronucleus assay.

Female rats were given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day beginning 15 days before mating and continuing through gestation. Effects observed in the high-dose group (with systemic exposure of 1.2 times the human systemic exposure following an intravenous dose of 4 mg, based on AUC comparison) included inhibition of ovulation and a decrease in the number of pregnant rats. Effects observed in both the mid-dose group (with systemic exposure of 0.2 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison) and high-dose group included an increase in preimplantation losses and a decrease in the number of implantations and live fetuses.

Before using Zoledronic acid, tell your doctor or pharmacist if you are allergic to it; or to other bisphosphonates (such as alendronate, risedronate); or if you have any other allergies. This product may contain inactive ingredients, which can cause allergic reactions or other problems. Talk to your pharmacist for more details. Before using this medication, tell your doctor or pharmacist your medical history, especially of: kidney problems, loss of too much body water (dehydration), and aspirin-sensitive asthma. Infrequently, people taking this class of medication (bisphosphonates) have had serious jawbone problems (osteonecrosis). Lack of proper dental hygiene, poorly fitting dentures, or certain dental procedures (such as tooth extraction, dental surgery) may increase your risk. Medical conditions (such as gum disease/infection, cancer, and anemia) might also increase the risk. If you develop jaw pain, tell your doctor and dentist immediately. Before having any surgery (especially dental procedures), tell your doctor and dentist about this medication and all other products you use (including prescription drugs, nonprescription drugs, and herbal products).This drug may make you dizzy. Do not drive, use machinery, or do any activity that requires alertness until you are sure you can perform such activities safely. Limit alcoholic beverages. This medication may cause severe kidney problems, especially in the elderly. Consult your doctor or pharmacist for more information. To help prevent harm to your kidneys, drink plenty of fluids unless otherwise directed by your doctor. (See also How to Use section.)This medication is not recommended for use during pregnancy. It may harm an

unborn baby. Consult your doctor for more details. It is unknown if this drug passes into breast milk. Because it may harm a nursing infant, breast-feeding while using this drug is not recommended. Consult your doctor before breast-feeding.

4.5 Interaction with other medicinal products and other forms of interaction

In clinical studies, Zoledronic acid injection 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 indicating a low like wood of pharmacokinetic drug interactions. However, no formal clinical interaction studies have been performed.

Caution is advised when bisphosphonates are administered with aminoglycosides, since these agents may have an additive effect, resulting in a lower serum calcium level for longer periods. This has not been reported in Zoledronic acid clinical trials. Caution is advise when Zoledronic acid is used with other potentially nephrotoxic medicinal drugs (renal functions be monitored). 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 Zoledronic acid is used in combination with thalidomide.

Carcinogenesis, Mutagenesis and Impairment of Fertility:

Carcinogenesis: Zoledronic acid was administered orally (gavage) to rats and mice for at least 104 weeks without evidence of carcinogenic potential. Chronic parenteral administration was not feasible given the potential of the compound to cause severe loyal irritation.

Mutagenesis: Zoledronic acid was not genotoxic in the Ames bacterial mutagenicity assay, in the Chinese hamster ovary cell assay or in the Chinese hamster gene mutation assay, with or without metabolic activation. Zoledronic acid was not genotoxic in the vivo rat micronucleus assay.

Impairment of Fertility: Female rats were given subcutaneous doses of Zoledronic acid of (0.01, 0.03, or 0.1 mg/kg/day beginning 15 days before mating and continuing through gestation. Effects observed in the high dose group (with systemic exposure of 1.2 times the

human systemic exposure following an intravenous dose of 4 mg, based on AUC comparison) included inhibition of ovulation and a decrease in the number of pregnant rats.

Pregnancy and lactation

Pregnancy (Category-D): There is no adequate data on the use of Zoledronic acid in pregnant women. Zoledronic acid should not be used during pregnancy. Women of child-bearing potential should be advised to avoid becoming pregnant.

Nursing Mothers: It is not known whether Zoledronic acid is excreted in human milk. Because many drugs are excreted in human milk and Zoledronic acid binds to bone, it should not be administered to a nursing woman.

Pediatric Use: The safety and effectiveness of Zoledronic acid in pediatric patients have not been established. Because of long time retention in bone, Zoledronic acid should only be used in children if the potential risk.

Geriatric Use: No significant differences in response rate or adverse reactions were seen in geriatric patients receiving Zoledronic acid as compared to younger patients**.**

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data on the use of zoledronic acid in pregnant women. Animal reproduction studies with zoledronic acid have shown reproductive toxicity. The potential risk for humans is unknown. Zoledronic acid should not be used during pregnancy. Women of child bearing potential should be advised to avoid becoming pregnant.

Breast-feeding

It is not known whether zoledronic acid is excreted into human milk. Zoledronic acid is contraindicated in breast-feeding women.

Fertility

Zoledronic acid was evaluated in rats for potential adverse effects on fertility of the parental and F1 generation. This resulted in exaggerated pharmacological effects considered to be related to the compound's inhibition of skeletal calcium metabolisation, resulting in periparturient hypocalcaemia, a bisphosphonate class effect, dystocia and early termination of the study. Thus these results precluded determining a definitive effect of zoledronic acid on fertility in humans.

4.7 Effects on ability to drive and use machines

Zoledronic acid injection has minor influence on the ability to drive or use machines. Adverse reactions such as dizziness (uncommon) and blurred vision (uncommon) have been reported. If affected patients should not drive or use machines.

4.8 Undesirable effects

Dizziness, headache, or flu-like symptoms (such as fever, chills, muscle/joint aches) may occur. If any of these effects persist or worsen, tell your doctor or pharmacist promptly. Remember that your doctor has prescribed this medication because he or she has judged that the benefit to you is greater than the risk of side effects. Many people using this medication do not have serious side effects. Tell your doctor right away if you have any serious side effects, including: increased or severe bone/joint/muscle pain, new or unusual hip/thigh/groin pain, jaw pain, eye/vision problems, numbness/tingling, muscle spasms, irregular heartbeat. Get medical help right away if you have any serious side effects, including: change in the amount of urine, seizures. A very serious allergic reaction to this drug is rare. However, get medical help right away if you notice any symptoms of a serious allergic reaction, including: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.

4.9 Overdose

Clinical experience with acute over dosage of Zoledronic Acid Injection is limited. Two patients received Zoledronic Acid Injection 32 mg over 5 minutes in clinical trials. Neither patient experienced any clinical nor laboratory toxicity. Over dosage may cause clinically significant hypocalcemia, hypophosphatemia, and hypomagnesemia. 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 sulfate, respectively.

In an open-label study of zoledronic acid 4 mg in breast cancer patients, a female patient received a single 48-mg dose of zoledronic acid in error. Two days after the overdose, the patient experienced a single episode of hyperthermia (38°C), which resolved after treatment. All other evaluations were normal, and the patient was discharged seven days after the overdose.

A patient with non-Hodgkin's lymphoma received zoledronic acid 4 mg daily on four successive days for a total dose of 16 mg. The patient developed paresthesia and abnormal liver function tests with increased GGT (nearly 100 U/L, each value unknown). The outcome of this case is not known.

In controlled clinical trials, administration of Zoledronic Acid Injection 4 mg as an intravenous infusion over 5 minutes has been shown to increase the risk of renal toxicity compared to the same dose administered as a 15-minute intravenous infusion. In controlled clinical trials, Zoledronic Acid Injection 8 mg has been shown to be associated with an increased risk of renal toxicity compared to Zoledronic Acid Injection 4 mg, even when given as a 15-minute intravenous infusion, and was not associated with added benefit in patients with hypercalcemia of malignancy.

5. Pharmacological properties

Mechanism of Action

The principal pharmacological action of Zoledronic acid is inhibition of bone resorption. It is one of the most potent inhibitors of osteoclast bone resorption, although the antiresorptive mechanism is not completely understood, several factors are thought to contribute to this action. In vitro Zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis. Zoledronic acid also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone. Zoledronic acid inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors. In addition to inhibiting osteoclast bone resorption, Zoledronic acid exerts direct antitumor effects on human myeloma and breast cancer cells, inhibiting their proliferation and inducing apoptosis. Zoledronic acid is antiangiogenic in animal tumor model. This anti -tumor efficacy may be enhanced when used in combination with other anticancer drugs.

5.1 Pharmacodynamic properties

Clinical studies in patients with hypercalcemia of malignancy (IICM) showed that single dose infusions of Zoledronic acid are associated with decrease in serum calcium and phosphorus and increase in urinary calcium and phosphorus excretion. Normalization of

serum calcium by day 4 was greater for Zoledronic acid 4 mg and 8 mg doses then Pamidronate.

Hypercalcemia of Malignancy

Osteoclastic hyperactivity resulting in excessive bone resorption is the underlying pathophysiological dearangement in hyperkalemia of malignancy (IICM), tumor induced hypercalcemia) and metastatic bone disease. Excessive release of calcium release of calcium into the blood as bone resorbed results in polyuria and gastrointestinal disturbances with progressive dehydration and decreasing glomerular filtration rate. This in turn, results in increased renal resorption of calcium, setting up a cycle of worsening systemic hypercalcemia. Reducing excessive bone resorption and adequate fluid administrations are, therefore, essential to the management of hypercalcemia.

5.2 Pharmacokinetic properties

Single or multiple (q 28days) 5-minutes infusion or 2, 4, 8 or 16 mg Zoledronic acid were given to 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%C_{max} 24 hours post infusion with population half-lives of $t_{1/2}$ alpha 0.24 hours and $t_{1/2}$ beta 1.87 hours for the early disposition phases of the drug. The terminal elimination phase of Zoledronic acid was 146 hours. The area under the plasma concentration versus time curve (AUC0-24h) of Zoledronic acid was dose proportional from 2 to 16 mg. The accumulation of Zoledronic acid measured over three cycles was low, with mean AUC0-4h ratios for cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36, respectively.

In-vitro and *In-vivo* studies showed low affinity of Zoledronic acid for the cellular components of human blood. Binding to human plasma proteins was approximately 22% and was independent of the concentration of Zoledronic acid.

Metabolism

Zoledronic acid does not inhibit human 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 feces, with the balance either recovered in the Urine or taken up bone, indicating that the drug is eliminated intact via the kidney.

Excretion

In patients with cancer and bone metastases on average (± s.d.) 39 ± 16% of the administration 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 days 2 to 20 post dose. The 0-24 hour renal clearance of Zoledronic acid was on average 3.7 ± 2.0 L/h.

Zoledronic acid clearance was reasonably independent of dose and demographic variables, with effects of body weight, gender and race, on clearance was dependent on creatinine clearance.

Special Populations: No pharmacokinetic data in patients with hypercalcemia.

Pediatrics: No pharmacokinetics data in pediatric patients.

Geriatrics: The pharmacokinetics of Zoledronic acid were not affected by age in patients with cancer and bone metastases aged 38 years to 84 years.

Race: The pharmacokinetics of Zoledronic acid were not affected by race in patients with cancer and bone metastases.

Hepatic insufficiency: There are no pharmacokinetic data in patients with impaired liver functions. Zoledronic acid is not cleared by liver therefore impaired liver function may not affect the pharmacokinetic of Zoledronic acid.

Renal insufficiency: Patients with mild to moderate (creatinine 50-80 mL/min) renal impairment showed an increase in plasma AUC of 26-27% whereas patients with moderate to severe renal impairment (creatinine clearance 30-50 mL/min) showed increase plasma AUC of 27-41%. Limited pharmacokinetic data are available for Zoledronic acid in patients with severe renal impairment (creatinine clearance <30 mL/min). Based on population PK/PD modeling, the risk of renal deterioration appears to increase with AUC, which is doubled at a creatinine clearance of 10mL/min.

6. Pharmaceutical particulars

6.1 List of excipients

Mannitol Ph. Eur, Sodium Citrate Dihydrate Ph. Eur, Water for Injection Ph. Eur.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30° C and protect from light.

6.5 Nature and contents of container

Glass Vials: 1's vials

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorisation Holder and Manufacturing Site Addresses

7.1 Name and Address of Manufacturer

Name	**: Aspiro Pharma Limited**
Business Address	: Survey No.321, Biotech Park, Phase III, Karkapatla, Markook Mandal, Siddipet District, Telangana (S)- 5002281, INDIA.
Country	: INDIA
Telephone	: +91 9959644022, 9959644077

7.2 Name and Address of Principal

Name	**: Aspiro Pharma Limited**
Business Address	: Survey No.321, Biotech Park, Phase III, Karkapatla, Markook Mandal, Siddipet District, Telangana (S)- 5002281,INDIA.
Country	: INDIA
Telephone	: +91 9959644022, 9959644077

8. Registration Number

Not applicable

9. Category for Distribution

Not applicable

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