1.3.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

DRONAMYL 4 mg/5 ml (Concentrate for dilution for infusion)

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each 15 ml vial contains 4 mg of zoledronic acid in a 5 ml solution.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Clear and colourless solution, free from particulate matter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

DRONAMYL 4 mg/5 ml injection is indicated:

- For the treatment of tumour-induced hypercalcaemia (HCM).
- DRONAMYL 4 mg/5 ml slows progression of skeletal conditions in adult patients when used in conjunction with appropriate antineoplastic therapy in patients with advanced carcinoma of the breast, prostate, lung and myeloma.

4.2 Posology and method of administration

Posology

Skeletal conditions in patients with advanced malignancies involving bone:

Adults and elderly:

- The recommended dose is 4 mg.
- The concentrate must further be diluted with 100 ml sterile 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 – 4 weeks.
- Patients should also be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily.

Treatment of tumour-induced hypercalcaemia:

Adults and elderly:

- The recommended dose in hypercalcaemia (albumin-corrected serum calcium ≥ 12,0 mg/dl or 3,0 mmol/l) is 4 mg.
- The concentrate must be diluted with 100 ml sterile 0,9 % *w/v* sodium chloride or 5 % *w/v* glucose solution and given as a single intravenous infusion in no less than 15 minutes.
- Patients must be maintained well hydrated prior to and following DRONAMYL 4 mg/5 ml.

Renal impairment:

Treatment of tumour-induced hypercalcaemia:

- DRONAMYL 4 mg/5 ml treatment in hypercalcaemia patients who also have severe renal impairment should be considered only after evaluating the risks and benefits of treatment.
- No dose adjustment is necessary in tumour-induced hypercalcaemia patients with serum creatinine < 400 micromol/l or < 4,5 mg/dl (see section 4.4).

Skeletal-related events in patients with advanced malignancies involving bone:

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- When initiating treatment with DRONAMYL 4 mg/5 ml in patients with multiple myeloma or metastatic bone lesions from solid tumours, serum creatinine levels and creatinine clearance (CLcr) should be determined. CLcr is calculated from serum creatinine levels using the Cockcroft-Gault formula.
- DRONAMYL 4 mg/5 ml is not recommended for patients presenting with severe renal impairment prior to initiation of therapy, which is defined for this population as CLcr < 30 ml/min.
- 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 30–60 ml/min, the following DRONAMYL 4 mg/5 ml doses are recommended (see section 4.4).

Baseline creatinine clearance (ml/min)	**DRONAMYL 4 mg/5 ml recommended dose***
> 60	4,0 mg
50–60	3,5 mg*
40–49	3,3 mg*
30–39	3,0 mg*

***** Doses have been calculated assuming target AUC of 0,66 (mg•hr/l) (CLcr = 75 ml/min). 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 DRONAMYL 4 mg/5 ml and treatment should be withheld, if renal function has deteriorated.

- Treatment may be resumed only when the creatinine level returned to within 10 % of the baseline value. DRONAMYL 4 mg/5 ml treatment should be resumed at the same dose as that given prior to treatment interruption.

Instructions on preparing reduced doses of DRONAMYL 4 mg/5 ml:

Withdraw an appropriate volume of the reconstituted solution (4 mg/5 ml) as needed:

4,4 ml	for 3,5 mg dose
4,1 ml	for 3,3 mg dose
3,8 ml	for 3,0 mg dose

- For information on the reconstitution and dilution of DRONAMYL 4 mg/5 ml refer to '*Instructions for use and handling'.*
- 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.

Instructions for use and handling:

- DRONAMYL 4 mg/5 ml concentrate for solution for infusion is for intravenous use only.
- Prior to administration, 5,0 ml concentrate from one vial or the volume of the concentrate withdrawn as required must be further diluted with 100 ml of calcium-free infusion solution (0,9 % *w/v* sodium chloride or 5 % w/*v* glucose solution).
- If refrigerated, the solution must be allowed to reach room temperature before administration (see section 4.2).

Incompatibilities:

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- Studies with glass bottles, as well as several types of infusion bags and infusion lines made from polyvinyl chloride, polyethylene and polypropylene (pre-filled with 0,9 % sodium chloride solution or 5 % glucose solution) showed no incompatibility with DRONAMYL 4 mg/5 ml.
- To avoid potential incompatibilities, DRONAMYL 4 mg/5 ml concentrate is to be diluted with 0,9 % sodium chloride solution or 5 % glucose solution.
- DRONAMYL 4 mg/5 ml concentrate must not be mixed with calcium-containing solutions such as Ringer's solution.

Method of administration

Intravenous route.

4.3 Contraindications

DRONAMYL 4 mg/5 ml is contraindicated in patients with a history of hypersensitivity to zoledronic acid, other biphosphonates or any of the inactive ingredients of DRONAMYL 4 mg/5 ml as listed in section 6.1.

DRONAMYL 4 mg/5 ml is also contraindicated in:

- Pregnancy and lactation (see section 4.6).
- Children aged 1 year to 17 years, as safety and efficacy have not been established.
- Severe renal function impairment (creatinine clearance less than 30 ml/min).

4.4 Special warnings and precautions for use

Patients must be assessed prior to administration of DRONAMYL 4 mg/5 ml to ensure that they are adequately hydrated.

Overhydration should be avoided in patients at risk of cardiac failure.

DRONAMYL 4 mg/5 ml should not be given together with other bisphosphonates since the combined effects of these medicines are unknown.

Standard hypercalcaemia-related metabolic parameters, such as serum levels of calcium, phosphate and magnesium, should be carefully monitored after initiating DRONAMYL 4 mg/5 ml therapy. If hypocalcaemia, hypophosphataemia, or hypomagnesaemia occurs, 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.

Renal impairment:

Patients with tumour-induced hypercalcaemia and evidence of deterioration in renal function should be appropriately evaluated.

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 – 3 months.

DRONAMYL 4 mg/5 ml has been associated with reports of renal dysfunction. Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of DRONAMYL 4 mg/5 ml and other bisphosphonates as well as use of other nephrotoxic medicines. While the risk is reduced with a dose of 4 mg of DRONAMYL 4 mg/5 ml administered over 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 4 mg zoledronic acid.

Increases in serum creatinine also occur in some patients with chronic administration of DRONAMYL 4 mg/5 ml 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 DRONAMYL 4 mg/5 ml. Upon initiation of treatment in patients with bone metastases with mild to moderate renal impairment, lower doses of DRONAMYL 4 mg/5 ml are recommended. In patients who show evidence of renal deterioration during treatment with DRONAMYL 4 mg/5 ml, treatment should only resume when the creatinine level returns to within 10 % of the baseline value (see section 4.2).
DRONAMYL 4 mg/5 ml treatment should be resumed at the same dose as that given prior to treatment interruption.
Because of the potential impact on renal function, the use of DRONAMYL 4 mg/5 ml is not recommended in patients with severe renal impairment (see section 4.3).

Hepatic impairment:
Limited clinical data is available in patients with severe hepatic insufficiency, therefore, no specific recommendations can be given for these patients.

Osteonecrosis of the jaw:
There have been reports of osteonecrosis of the jaw (ONJ) in patients with cancer receiving treatment regimens including DRONAMYL 4 mg/5 ml.
The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth, except in medical emergencies.
Many of these patients were also receiving chemotherapy and corticosteroids. Most of the cases reported have been associated with dental procedures (tooth extraction). Many had signs of local infection including osteomyelitis.

A dental examination with appropriate preventative dentistry and an individual benefit-risk assessment is recommended prior to treatment with bisphosphonates in patients with

concomitant risk factors. If possible, patients should avoid invasive dental procedures while receiving DRONAMYL 4 mg/5 ml.

The following risk factors should be considered when evaluating an individual's risk of developing ONJ:

- Potency of the bisphosphonate (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bisphosphonate.
- Cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking.
- Concomitant therapies: chemotherapy, angiogenesis inhibitors, radiotherapy to neck and head, corticosteroids.
- History of dental disease, poor oral hygiene, periodontal disease, invasive dental procedures (e.g. tooth extractions) and poorly fitting dentures.

All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, or non-healing of sores or discharge during treatment with DRONAMYL 4 mg/5 ml. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to zoledronic acid administration. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw.

The management plan for patients who develop ONJ should be set up in close collaboration between the treating doctor and a dentist or oral surgeon with expertise in ONJ. Temporary

interruption of zoledronic acid treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Osteonecrosis of the external auditory canal:

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

Musculoskeletal pain:

In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain have been reported, however, such reports have been infrequent. 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 bisphosphonate treatment.

Atypical fractures of the femur:

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with DRONAMYL 4 mg/5 ml therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral, therefore, the contra-lateral femur should be examined in DRONAMYL 4 mg/5 ml-treated patients who

have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of DRONAMYL 4 mg/5 ml therapy in patients suspected to have an atypical femur fracture should be considered pending on evaluation of the patient. The patient should receive appropriate orthopedic care.
During DRONAMYL 4 mg/5 ml treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

Hypocalcaemia:

Hypocalcaemia has been reported in patients treated with DRONAMYL 4 mg/5 ml. Cardiac arrhythmias and neurologic adverse events (including convulsions, hypoaesthesia and tetany) have been reported secondary to cases of severe hypocalcaemia. Cases of severe hypocalcaemia requiring hospitalisation have been reported. In some instances, the hypocalcaemia may be life-threatening. Caution is advised when DRONAMYL 4 mg/5 ml is administered with medicines known to cause hypocalcaemia, as they may have a synergistic effect resulting in severe hypocalcaemia. Serum calcium should be measured and hypocalcaemia must be corrected before initiating DRONAMYL 4 mg/5 ml therapy. Patients should be adequately supplemented with calcium and vitamin D.

Atrial fibrillation:

There are reports of atrial fibrillation in post-menopausal women.

Acute phase reaction:

Acute phase reaction consists of a constellation of symptoms that includes fever, myalgia, headache, extremity pain, nausea, vomiting, diarrhoea and arthralgia. The onset time is ≤ 3 days post-DRONAMYL 4 mg/5 ml infusion, and the reaction is also referred to using the terms “flu-like” or “post-dose” symptoms.

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4.5 Interaction with other medicines and other forms of Interaction

Caution is advised when DRONAMYL 4 mg/5 ml is administered with aminoglycosides, calcitonin or loop diuretics, since both medicines may have an additive effect, resulting in a lower serum calcium level for longer periods than required.

Caution is indicated when DRONAMYL 4 mg/5 ml is used with other potentially nephrotoxic medicines. Attention should also be paid to the possibility of hypomagnesaemia developing during treatment.

Caution is advised when DRONAMYL 4 mg/5 ml is administered with anti-angiogenic medicines as an increase in incidence of ONJ has been observed in patients treated concomitantly with these medicines.

In multiple myeloma patients, the risk of renal dysfunction may be increased when DRONAMYL 4 mg/5 ml is used in combination with thalidomide.

Cancer patients receiving treatment regimens including biphosphates such as DRONAMYL 4 mg/5 ml and also receiving chemotherapy and corticosteroids may be at risk of osteonecrosis of the jaw (see section 4.4).

There may be an increased risk of hypocalcaemia when DRONAMYL 4 mg/5 ml is used with loop diuretics.

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4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of child-bearing potential should be advised to avoid becoming pregnant and advised of the potential hazard to the foetus while receiving DRONAMYL 4 mg/5 ml. There may be a risk of foetal harm (e.g. skeletal and other abnormalities) if a woman becomes pregnant (see section 4.3) while receiving bisphosphonate therapy.

Pregnancy

DRONAMYL 4 mg/5 ml should not be used during pregnancy as safety has not been established (see section 4.3).

Breastfeeding

DRONAMYL 4 mg/5 ml should not be used during breastfeeding, as safety has not been established (see section 4.3).

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness and somnolence reported with the use of DRONAMYL 4 mg/5 ml may influence the ability to drive or use machinery and caution is therefore necessary. The patients should therefore be careful when driving, using machinery or performing other tasks that need full attention. It is not always possible to predict to what extent DRONAMYL 4 mg/5 ml may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the extent to which DRONAMYL 4 mg/5 ml affects them.

4.8 Undesirable effects

Summary of the safety profile

Within three days after DRONAMYL 4 mg/5 ml administration, an acute phase reaction has commonly been reported, with symptoms including bone pain, fever, fatigue, arthralgia, myalgia, rigors and arthritis with subsequent joint swelling. These symptoms usually resolve within a few days (see section 4.4).

The following are the important identified risks with DRONAMYL 4 mg/5 ml in the approved indications: renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, atrial fibrillation, anaphylaxis, interstitial lung disease.
The frequencies for each of these identified risks are shown in the table below.

Tabulated list of adverse reactions

Blood and lymphatic system disorders		
	Frequent:	Anaemia
	Less frequent:	Thrombocytopenia, leucopenia, pancytopenia
Immune system disorders		
	Less frequent:	Hypersensitivity reaction, angioedema
Psychiatric disorders		
	Less frequent:	Anxiety, sleep disturbance, confusion
Nervous system disorders		
	Frequent:	Headache

	Less frequent:	Dizziness, paraesthesia, taste disturbance, hypoaesthesia, hyperaesthesia, tremor, somnolence, convulsions, tetany (secondary to hypocalcaemia)
Eye disorders		
	Frequent:	Conjunctivitis
	Less frequent:	Blurred vision, scleritis, orbital inflammation, uveitis, episcleritis
Cardiac disorders		
	Less frequent:	Hypertension, hypotension, atrial fibrillation, hypotension leading to syncope or circulatory collapse, bradycardia, cardiac dysrhythmia (secondary to hypocalcaemia)
Respiratory, thoracic and mediastinal disorders		
	Less frequent:	Dyspnoea, cough, bronchoconstriction, interstitial lung disease
Gastrointestinal disorders		
	Frequent:	Nausea, vomiting, anorexia, decreased appetite
	Less frequent:	Diarrhoea, constipation, abdominal pain, dyspepsia, stomatitis, dry mouth
Skin and subcutaneous tissue disorders		
	Less frequent:	Pruritus, rash (including erythematous and macular rash), increased sweating
Musculoskeletal, connective tissue and bone disorders		

	Frequent:	Bone pain, myalgia, arthralgia, generalised pain, joint stiffness
	Less frequent:	Muscle cramps, osteonecrosis of the jaw, osteonecrosis of the auditory canal
Renal and urinary disorders		
	Frequent:	Renal impairment
	Less frequent:	Acute renal failure, haematuria, proteinuria, acquired Fanconi syndrome
General disorders and administration site conditions		
	Frequent:	Fever, flu-like syndrome (including fatigue, rigors, malaise and flushing)
	Less frequent:	Asthenia, peripheral oedema, injection site reactions (including pain, irritation, swelling, induration), chest pain, weight increase, anaphylactic reaction/shock, urticarial, arthritis and joint swelling as a symptom of acute phase reaction
Investigations		
	Frequent:	Hypophosphataemia, blood creatinine and blood urea increased, hypocalcaemia
	Less frequent:	Hypomagnesaemia, hypokalaemia, hyperkalaemia, hypernatraemia

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Description of selected adverse reactions

Renal function impairment:

Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of DRONAMYL 4 mg/5 ml or other bisphosphonates, as well as concomitant use of nephrotoxic medicines or using a shorter infusion time than currently recommended. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of DRONAMYL 4 mg/5 ml (see section 4.4).

Osteonecrosis of the jaw:

Cases of osteonecrosis (primarily of the jaws) have been reported predominantly in cancer patients treated with bisphosphonates, such as DRONAMYL 4 mg/5 ml. Many of these patients had signs of local infection including osteomyelitis. 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. anaemia, coagulopathies, infection, pre-existing oral disease). Although causality cannot be determined, it is prudent to avoid dental surgery as recovery may be prolonged (see section 4.4).

Osteonecrosis of other anatomical sites:

Cases of osteonecrosis of other anatomical sites including the hip, femur and external auditory canal have been reported predominantly in adult cancer patients treated with bisphosphonates, including DRONAMYL 4 mg/5 ml.

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Acute phase reaction:

This adverse drug reaction consists of a constellation of symptoms that includes fever, fatigue, bone pain, chills, myalgia, headache, extremity pain, nausea, vomiting, diarrhoea, arthralgia and arthritis with subsequent joint swelling. The onset time is ≤ 3 days post-DRONAMYL 4 mg/5 ml infusion, and the reaction is also referred to using the terms “flu-like” or “post-dose” symptoms. These symptoms usually resolve within a few days.

Atypical fractures of the femur:

During post-marketing experience the following reactions have been reported (frequency rare):

Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction).

Hypocalcaemia-related ADRs:

Hypocalcaemia is an important identified risk with DRONAMYL 4 mg/5 ml in the approved indications. Based on post-marketing cases, there is sufficient evidence to support an association between DRONAMYL 4 mg/5 ml therapy, the reported event of hypocalcaemia, and the secondary development of cardiac dysrhythmia. Furthermore, there is evidence of an association between hypocalcaemia and secondary neurological events reported in these cases including: convulsions, hypoaesthesia and tetany (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the “**6.04 Adverse Drug Reactions Reporting Form**”, found online under SAHPRA’s publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (*see section 4.8)*.

Clinical experience with acute overdose is limited and there is no known specific antidote to DRONAMYL 4 mg/5 ml.

Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION:

A 32.2 Other

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

Zoledronic acid is a bisphosphonate acting primarily on bone and an inhibitor of osteoclastic bone resorption.

The antiresorptive mechanism is not fully understood and several factors are thought to contribute to this action. *In vitro,* zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis. Osteoclastic resorption of mineralised bone and cartilage through its binding to bone is blocked by zoledronic acid. Increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumours are inhibited by zoledronic acid.

5.2 Pharmacokinetic properties

Absorption:

Area under the plasma concentration versus time curve (AUC) of zoledronic acid was dose proportional from 2 to 16 mg. After initiating the infusion of zoledronic acid, the plasma concentrations of zoledronic acid 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 zoledronic acid on day 28.

Intravenously administered zoledronic acid is eliminated by a triphasic process: rapid biphasic disappearance from the systemic circulation, with half-lives of $t_{½\alpha}$ 0,24 and $t_{½\beta}$ 1,87 hours, followed by a long elimination phase with a terminal elimination half-life of $t_{½\gamma}$ 146 hours. There was no accumulation of zoledronic acid in plasma after multiple doses given every 28 days. Zoledronic acid is not metabolised and is excreted unchanged via the kidney. Over the first 24 hours, 39 ± 16 % of 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.

Elimination:

Renal: approximately 44 %.

Renal clearance was 3,7 ± 2,0 litres per hour. Remainder is substance bound to bone, and is slowly released back into systemic circulation, giving rise to the 146-hour terminal half-life.

Patients with mild and moderate renal impairment showed an increased AUC of 15 % and 43 %, respectively. The risk of renal deterioration appears to increase with AUC, which is doubled at creatinine clearance of 10 ml per minute.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate

Sodium hydroxide (pH adjuster)

Hydrochloric acid, concentrated (pH adjuster)

Water for injections

6.2 Incompatibilities

Studies with glass bottles, as well as several types of infusion bags and infusion lines made from polyvinylchloride, polyethylene and polypropylene (pre-filled with 0,9 % sodium chloride solution or 5 % glucose solution), showed no incompatibility with DRONAMYL 4 mg/5 ml.
To avoid potential incompatibilities, DRONAMYL 4 mg/5 ml concentrate is to be diluted with 0,9 % sodium chloride solution or 5 % glucose solution. DRONAMYL 4 mg/5 ml concentrate must not be mixed with calcium-containing solutions such as Ringer's solution.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 ˚C.

Protect from light.

Do not remove ampoule from carton until required for use.

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 healthcare 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. Do not freeze the reconstituted solution.

Only clear solution free from particles and discoloration should be used.

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6.5 Nature and contents of container

15 ml colourless type 1 glass vial containing 4 mg of zoledronic acid in a 5 ml solution with a bromobutyl rubber stopper coated with a tetrafluoroethylene and ethylene copolymer and aluminium crimp cap with plastic flip-off button. The vials are packed in 1's in a cardboard carton.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

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

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Isando

Gauteng, 1601

8 REGISTRATION NUMBER(S)

47/32.2/0039

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 May 2019

10 DATE OF REVISION OF TEXT

09 February 2024