Applicant : Biomab Innovation (Pty) Ltd
Proprietary name : Eurodron
Dosage form and strength : Concentrate for solution for infusion
Date of submission : 26 April 2024
Approval date : 13 January 2025

APPROVED PROFESSIONAL INFORMATION FOR EURODRON

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

EURODRON 4 mg/5 ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial with 5 ml concentrate contains 4 mg zoledronic acid as zoledronic acid monohydrate.

Excipient: Mannitol, sodium citrate dihydrate, water for injection.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless, sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

EURODRON is used in the treatment of tumour-induced hypercalcaemia (HCM).

EURODRON slows the 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

A dose of 4 mg EURODRON is recommended in the treatment of the above. The concentrate must be further diluted with 100 ml sterile 0,9 % m/v sodium chloride or 5 % m/v glucose solution, and given over no less than 15 minutes by intravenous infusion every 3 to 4 weeks. An oral calcium supplement of 500 mg and 400 IU vitamin D daily should also be administered.

Treatment of tumour-induced hypercalcaemia (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 EURODRON. The concentrate must be diluted with 100 ml sterile 0,9 % m/v sodium chloride or 5 % m/v glucose solution and given as a single intravenous infusion of no less than 15 minutes. Patients must be maintained well-hydrated prior to and following administration of EURODRON.

Renal impairment:

Treatment of tumour-induced hypercalcaemia (HCM)

EURODRON treatment in patients with HCM and who also have severe renal impairment should be considered only after evaluating the risks and benefits of treatment. Patients with serum creatinine > 400 µmol/l or > 4,5 mg/dl were excluded. No dose adjustment is required in HCM patients with serum creatinine < 400 µmol/l or < 4,5 mg/dl (see **section 4.4**).

Skeletal related events in patients with advanced malignancies involving bone

When initiating treatment with EURODRON 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 Cockcraft-Gault formula. EURODRON is not recommended for patients presenting with severe renal impairment (CrCl < 30 ml/min) prior to initiation of therapy.

In patients with bone metastases presenting with mild to moderate renal impairment (CrCl 30 – 60 ml/min) prior to initiation of therapy, the following doses are recommended (see also **Section 4.4**):

Table 1:

Baseline creatinine clearance (ml/min)	**EURODRON 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) (CrCl = 75 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 EURODRON. Treatment should be withheld if renal function has deteriorated. Renal deterioration can be defined as follows:

- for patients with normal baseline serum creatinine (< 1,4 mg/dl or 123,76 mmol/l), an increase of ≥ 0,5 mg/dl or 44,2 mmol/l.
- for patients with an abnormal baseline creatinine (> 1,4 mg/dl or 123,76 mmol/l), an increase of ≥ 1,0 mg/dl or 88,4 mmol/l.

EURODRON may only be resumed when the creatinine level has returned to within 10 % of the baseline value (see **section 4.4**). EURODRON should be resumed at the same dose as that prior to treatment interruption.

For instructions on preparing reduced doses of EURODRON see **section 6.6**.

4.3 Contraindications

- Hypersensitivity to zoledronic acid, other bisphosphonates or any of the inactive ingredients in the formulation of EURODRON (see **section 6.1**).
- Severe impairment of renal function (≤ 30 ml/min).
- Pregnancy and lactation.

4.4 Special warnings and precautions for use

General

It is important to ensure adequate hydration before and after administration of EURODRON as dehydration predisposes to deterioration in renal function.

After initiating EURODRON treatment serum levels of calcium, phosphate, magnesium as well as serum creatinine should be carefully monitored as standard metabolic parameters of hypercalcaemia. Short-term supplemental therapy may be necessary if hypocalcaemia, hypophosphataemia, or hypomagnesaemia occurs. Untreated hypercalcaemia patients generally have some degree of renal function impairment, therefore careful renal function monitoring should be considered.

Renal insufficiency

Patients with HCM with evidence of deterioration in renal function should be appropriately evaluated. Consideration should be given as to whether the potential benefit of continued treatment with EURODRON 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 2–3 months.

Bisphosphonates as a class, including EURODRON, have been associated with reports of renal dysfunction. Renal function must be monitored. Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of EURODRON or other bisphosphonates as well as use of nephrotoxic medicine, or using a shorter infusion time than currently recommended. While the risk is reduced with a single dose of EURODRON 4 mg/5 ml 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 4 mg zoledronic acid.) In some patients with chronic administration of EURODRON, increases in serum creatinine also occur 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 EURODRON. Upon initiation of treatment in patients with bone metastases with mild to moderate renal impairment, lower doses of EURODRON are recommended. In patients who show evidence of renal deterioration during treatment, EURODRON should only be resumed when the creatinine level returns to within 10 % of baseline value (see **section 4.2**).

In view of the potential impact of bisphosphonates, including EURODRON, on renal function and the lack of extensive clinical safety data in patients with severe renal impairment (serum creatinine ≥ 400 µmol/l for patients with HCM and ≥ 265 µmol/l 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 EURODRON is not recommended in patients with severe renal impairment (see **section 4.3**).

Hepatic insufficiency

Limited clinical data are available in patients with severe hepatic insufficiency, no specific recommendations can be given for this patient population.

Osteonecrosis

Osteonecrosis of the jaw

Osteonecrosis of the jaw has been reported predominantly in patients with cancer receiving treatment regimens, including bisphosphonates such as EURODRON. 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 preventative dentistry should be considered prior to treatment with bisphosphonates, such as EURODRON, in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene, anaemia, coagulopathies, infection, pre-existing oral disease). While on treatment, these patients should avoid invasive dental procedures if possible.

Hypotension may lead to syncope or circulatory collapse, primarily in patients with underlying risk factors.

For patients who develop osteonecrosis of the jaw while treated with EURODRON,

dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of EURODRON treatment reduces the risk of osteonecrosis of the jaw. Clinical judgement of the treating medical practitioner should guide the management plan of each patient based on an individual benefit/risk assessment.

Osteonecrosis of other anatomical sites

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 in patients taking EURODRON. 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 EURODRON or another bisphosphonate.

Atypical fractures of the femur

Atypical, low energy fractures of the sub-trochanteric and proximal femoral shaft have been reported with long-term use (usually longer than 3 years) in patients treated with EURODRON. Some were stress fractures (also reported as insufficiency fractures) occurring in the absence of apparent trauma.

Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a fracture occurred. Approximately one third of these fractures were bilateral, therefore, the contralateral femur should be examined in patients who have sustained a femoral shaft stress fracture and receive appropriate orthopaedic care.

EURODRON treatment should be stopped in patients with stress fractures and they should receive appropriate orthopaedic care.

Hypocalcaemia

Hypocalcaemia has been reported in patients treated with EURODRON. 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 (see **section 4.8**). Caution is advised when EURODRON is administered with medicinal products known to cause hypocalcaemia, as they may have a synergistic effect resulting in severe hypocalcaemia (see **section 4.5**). Serum calcium should be measured and hypocalcaemia must be corrected before initiating EURODRON therapy. Patients should be adequately supplemented with calcium and vitamin D.

Cardiac failure

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

Paediatric patients

The safety and efficacy of EURODRON in paediatric patients have not been established.

4.5 Interactions with other medicines and other forms of interaction

EURODRON has been administered concomitantly with commonly used anticancer agents, diuretics, antibiotics and analgesics without clinically apparent interactions occurring.

Concomitant use of EURODRON with aminoglycosides may have an additive effect, with a lower serum calcium level for prolonged periods.

Medicines exhibiting nephrotoxicity should be used with caution during and after EURODRON treatment. 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 EURODRON is used in combination with thalidomide.

Individual benefit/risk needs to be assessed in patients on chemotherapy and/or corticosteroid treatment with concomitant use of EURODRON as they may be at risk for osteonecrosis of the jaw (see **section 4.4**).

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 (see section 5.3). The potential risk for humans is unknown. EURODRON 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. EURODRON is contraindicated in breast-feeding women (see section 4.3).

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

No studies with EURODRON on the effects on the ability to drive and use machines have been performed. Care should be exercised when feeling dizzy, tired or drowsy after treatment with EURODRON.

4.8 Undesirable effects

Summary of the safety profile

With EURODRON administration, an acute phase reaction has frequently 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 description of selected adverse reactions).

The following are the important identified risks with EURODRON 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 below.

Tabulated list of adverse reactions

Blood and lymphatic system disorders	
Frequent:	Anaemia.
Less frequent:	Thrombocytopenia, leukopenia, pancytopenia.
Immune system disorders	
Less frequent:	Hypersensitivity reaction, Angioneurotic oedema.
Psychiatric disorders	
Less frequent:	Anxiety, sleep disturbance insomnia, confusion, depression.

Nervous system disorders	
Frequent:	Headache.
Less frequent:	Dizziness, paraesthesia, taste disturbance, dysgeusia, hypoaesthesia, hyperaesthesia, tremor, somnolence, convulsions, hypoaesthesia and tetany (secondary to hypocalcaemia).
Eye disorders	
Frequent:	Conjunctivitis.
Less frequent:	Blurred vision, scleritis and orbital inflammation, uveitis, episcleritis.
Cardiac disorders	
Less frequent:	Atrial fibrillation, bradycardia, cardiac arrhythmia (secondary to hypocalcaemia).
Vascular disorders	
Less frequent:	Hypertension, hypotension, hypotension leading to syncope or circulatory collapse.
Respiratory, thoracic and mediastinal disorders	
Less frequent:	Dyspnoea, cough, bronchoconstriction, (interstitial lung disease), upper respiratory tract infection, sore throat.
Gastrointestinal disorders	
Frequent:	Nausea, vomiting, decreased appetite.
Less frequent:	Diarrhoea, constipation, abdominal pain,

	dyspepsia, stomatitis, dry mouth, taste perversion, thirst.
Skin and subcutaneous tissue disorders	
Less frequent:	Pruritus, dermatitis, rash (including erythematous and macular rash), increased swelling. moniliasis.
Musculoskeletal and connective tissue disorders	
Frequent:	Bone pain, myalgia, arthralgia, generalised pain.
Less frequent:	Muscle spasms, osteonecrosis of the jaw, osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction) and other anatomical sites including femur and hip.
Renal and urinary disorders	
Frequent:	Renal impairment, renal toxicity, urinary tract infection.
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, urticaria, 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.

Description of selected adverse reactions

Renal function impairment

EURODRON 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 EURODRON or other isphosphonates, as well as concomitant use of nephrotoxic medicinal products 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 4 mg zoledronic acid (see **section 4.4).**

Osteonecrosis of the jaw

Cases of osteonecrosis of the jaw have been reported, predominantly in cancer patients treated with medicinal products that inhibit bone resorption, such as EURODRON (see **section 4.4).** Many of these patients were also receiving chemotherapy and corticosteroids and had signs of local infection including osteomyelitis. The majority of the reports refer to cancer patients following tooth extractions or other dental surgeries.

Acute phase reaction

This adverse drug reaction consists of a constellation of symptoms that includes fever, myalgia, headache, extremity pain, nausea, vomiting, diarrhoea arthralgia and arthritis with subsequent joint swelling. The onset time is ≤ 3 days post-EURODRON infusion, and the reaction is also referred to using the terms “flu-like” or “post-dose” symptoms.

Atypical fractures of the femur

During post-marketing experience the following reactions have been reported (less frequent): Atypical subtrochanteric and diaphyseal femoral fractures (bisphopsphonate class adverse reaction).

Hypocalcaemia-related ADRs

Hypocalcaemia is an important identified risk with EURODRON in the approved indications. Based on the review of both clinical trial and post-marketing cases, there is sufficient evidence to support an association between EURODRON therapy, the reported event of hypocalcaemia, and the secondary development of cardiac arrhythmia. 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**). **(3H.5)**

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. Health care provders 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

Symptoms:

Hypocalcaemia, hypophosphataemia, hypomagnesaemia.

Treatment:

There is no known specific antidote to EURODRON. Treatment is generally symptomatic and supportive. Reductions in serum levels of calcium, phosphate and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate and magnesium sulphate respectively.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Zoledronic acid is a bisphosphonate that acts primarily on bone, inhibiting osteoclastic bone resorption.

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* indicates that it may have anti-metastatic properties.

5.2 Pharmacokinetic properties

After initiating the infusion of zoledronic acid, the plasma concentration of zoledronic acid increases, and achieves its peak at the end of the infusion period. This is followed by a 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 in two stages: rapid biphasic disappearance from the systemic circulation, with half-lives of 0,24 and 1,87 hours, followed by a long elimination phase with a terminal elimination half-life $T_{1/2y}$ of 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 primarily bound to bone tissue. From the bone tissue it is released very slowly back into the systemic circulation and eliminated via the kidney with a half-life of at least 167 hours. The total body clearance is 5,04 ± 2,5 l/h independent of dose, and is unaffected by gender, age, race, and body weight.

Increasing the infusion time from 5 to 15 minutes caused a 30 % decrease in the zoledronic acid concentration at the end of the infusion, but had no effect on the area under the plasma concentration versus time curve.

The interpatient variability in pharmacokinetic parameters for zoledronic acid is high.

No pharmacokinetic data for zoledronic acid are available in patients with hypercalcaemia or in patients with hepatic insufficiency. Zoledronic acid does not inhibit human cytochrome P450 enzymes *in vitro* and shows no biotransformation. 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 represents 75 ± 33 % of the creatinine clearance, which showed a mean of 84 ± 29 ml/min (range 22 to 143 ml/min) in cancer patients. 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 of 84 ml/min. Only limited pharmacokinetic data are available in patients with severe renal insufficiency (creatinine clearance < 30 ml/min).

Zoledronic acid shows no affinity for the cellular components of blood. Plasma protein binding is approximately 56 % and independent of the concentration of zoledronic acid.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Sodium citrate dihydrate

Water for injection

6.2 Incompatibilities

Glass bottles, as well as several types of infusion bags and infusion lines made from polyvinylchloride, polyethylene and polypropylene (pre-filled with 0,9 % m/v sodium chloride solution or 5 % m/v glucose solution), showed no incompatibility with zoledronic acid. EURODRON reconstituted solution must not be mixed with calcium-containing solutions such as Lactated Ringer's solution.

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

36 months

After aseptic dilution, it is preferable to use the diluted product immediately. If not used immediately, the solution may be stored in a refrigerator at 2 to 8 °C. The duration and conditions of storage prior to use are the healthcare provider's responsibility.

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

6.4 Special precautions for storage

Store at or below 25 °C.

Do not freeze.

KEEP OUT OF REACH OF CHILDREN.

For storage conditions of the diluted medicine, see section 6.3.

6.5 Nature and contents of container

- Clear, colourless, cycloolefine, copolymer plastic vial with a grey, type I bromobutyl rubber stopper (20 mm) and sealed with an aluminium seal with a white polypropylene flip-off cap.
- Clear Type I silicon dioxide inner coated glass vials, capped with rubber stoppers and sealed with aluminium cap with flip off seals.
- Clear Type I borosilicate glass vials (20 mm) and sealed with rubber stoppers, type I, bromobutyl, 20 mm injection stopper.
- Packs containing 1, 4 or 10 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions on preparing reduced doses of EURODRON:

Withdraw an appropriate volume of the concentrate for 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

The withdrawn amount of liquid concentrate must be further diluted. For information on the reconstitution and dilution of EURODRON, see **Instructions for use and handling**.

Instructions for use and handling:

EURODRON 4 mg/5 ml concentrate for solution for infusion is for intravenous use only.

Prior to administration the required volume of the concentrate should be withdrawn from the vial (see **Instructions on preparing reduced doses of EURODRON** if a dosage of less than

4 mg is required). The required volume is then further diluted with 100 ml of calcium-free infusion solution (sterile 0,9 % *m/v* sodium chloride solution or 5 % m/v glucose solution).

If refrigerated, the solution must be allowed to reach room temperature before administration (see **section 6.3**).

When administered, the solution must be given as a single intravenous infusion over no less than 15 minutes (see **section 4.2**).

7 HOLDER OF CERTIFICATE OF REGISTRATION

Biomab Innovation (Pty) Ltd

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8 REGISTRATION NUMBERS

47/32.16/1126

9 DATE OF FIRST AUTHORISATION

16 February 2017

10 DATE OF REVISION OF TEXT

13 January 2025

11 DOSIMETRY

Not applicable

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable