FINAL PACKAGE INSERT FOR ZOMEDRON

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

ZOMEDRON (Injection)

COMPOSITION:

Each vial contains zoledronic acid monohydrate equivalent to zoledronic acid anhydrous 4 mg.

PHARMACOLOGICAL CLASSIFICATION:

A 34 Other.

PHARMACOLOGICAL ACTION:

Zoledronic acid is a bisphosphonate which primarily acts on the bone by inhibiting bone resorption without adversely affecting the formation, mineralisation or mechanical properties of bone. The selective action of zoledronic acid on bone is based on the affinity for mineralised bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity is still unclear. 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.*

Zoledronic acid reduces the invasion of human breast cancer cells through extracellular matrix *in vitro,* indicating that it may have anti-metastatic properties.

INDICATIONS:

ZOMEDRON is indicated for:

- Treatment of tumour-induced hypercalcaemia (HCM).
- Osteolytic lesions of multiple myeloma, in conjunction with standard antineoplastic therapy.
- Breast carcinoma with metastatic bone lesions in combination with appropriate anticancer therapy.
- Prostate carcinoma in patients with bone metastases who have increased prostate specific antigen (PSA) levels despite hormonal therapy.

CONTRA-INDICATIONS:

ZOMEDRON is contra-indicated in the following:

- Patients with clinically significant hypersensitivity to zoledronic acid, other bisphosphonates or any of the excipients in the formulation of **ZOMEDRON**.
- Severe impairment of renal function.
- Severe impairment of liver function.
- Pregnancy and lactation.

WARNINGS:

Patients should be assessed prior to administration of **ZOMEDRON** to assure

adequate hydration. Over-hydration should be avoided in patients at risk of cardiac failure.

Standard hypercalcaemia-related metabolic parameters, such as serum levels of calcium, phosphate, magnesium, as well as serum creatinine should be carefully monitored after initiating **ZOMEDRON** therapy. If hypocalcaemia, hypophosphataemia, or hypomagnesaemia occur, short term supplemental therapy may be necessary. Bisphosphonates as a class, including **ZOMEDRON**, have been associated with reports of renal dysfunction. Factors that may increase the potential for deterioration in renal function include pre-existing renal impairment and chronic administration of **ZOMEDRON** at the 8 mg dose or using a shorter infusion time than currently recommended.

Renal function should be monitored appropriately during therapy with **ZOMEDRON** considering individual risk factors, and patients with evidence of deterioration in renal function should be appropriately evaluated with consideration given as to whether the potential benefit of continued treatment with **ZOMEDRON** outweighs the possible risk.

In view of the potential impact of bisphosphonates, including **ZOMEDRON**, on renal function, the use of **ZOMEDRON** is not recommended in this population (see **"CONTRA-INDICATIONS"**).

In patients with severe hepatic insufficiency, no specific recommendations can be given for this patient population (see **"CONTRA-INDICATIONS"**).

Increases in serum creatinine also occur in some patients with chronic administration of **ZOMEDRON** at recommended doses.

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

INTERACTIONS:

ZOMEDRON can be administered concomitantly with commonly used anticancer agents, diuretics, antibiotics and analgesics without apparent interactions occurring. Zoledronic acid shows no appreciable binding to plasma proteins and human P450 enzymes *in vitro.* Caution is advised when **ZOMEDRON** is administered with aminoglycosides, 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 hypomagnesaemia developing during treatment.

PREGNANCY AND LACTATION:

The use of **ZOMEDRON** during pregnancy and lactation is not recommended as safety and efficacy have not been established. **ZOMEDRON** should not be used during pregnancy (see **"CONTRA-INDICATIONS"**).

DOSAGE AND DIRECTIONS FOR USE:

For the treatment of:

- *Osteolytic lesions of multiple myeloma, in conjunction with standard antineoplastic therapy.*

- *Breast carcinoma with metastatic bone lesions in combination with appropriate anticancer therapy.*
- *Prostate carcinoma in patients with bone metastases who have increased prostate specific antigen (PSA) levels despite hormonal therapy.*

Adults and the elderly: The recommended dose in the treatment of the above is 4 mg reconstituted and further diluted **ZOMEDRON** (diluted with 100 ml 0,9 % w/v sodium chloride or 5 % w/v glucose solution), given as a 15-minute intravenous infusion every 3 to 4 weeks.

For the treatment of tumour-induced hypercalcaemia (HCM): Adults and elderly: The recommended dose in hypercalcaemia (albumin-corrected serum calcium $\geq$ 12,0 mg/dl or 3,0 mmol/l) is 4 mg reconstituted and further diluted **ZOMEDRON** (diluted with 100 ml 0,9 % sodium chloride or 5 % glucose solution), given as a single 15-minute intravenous infusion. Patients must be maintained well hydrated prior to and following administration of **ZOMEDRON**.

Retreatment of tumour-induced hypercalcaemia (HCM):

Patients exhibiting complete or partial response initially may be retreated with **ZOMEDRON** if serum calcium does not return to normal or does not remain normal after initial treatment. However, at least one week must elapse before retreatment to allow for a full response to the initial dose. The solution for this infusion is prepared by reconstituting two vials of **ZOMEDRON** 4 mg, combining them and then further diluting with 100 ml 0,9 % w/v sodium chloride or 5 % w/v glucose solution.

The median time to relapse is 30 days with a dose of 4 mg and 40 days with a dose of 8 mg **ZOMEDRON**.

Renal impairment:

Adjustment of dosage or infusion time is not required in patients with mild or moderate renal impairment (serum creatinine less than 400 µmol/l or less than 4,5 mg/dl, or calculated creatinine clearance by Cockcroft-Gault formula of more than 30 ml/min).

Reconstitution:

ZOMEDRON is for intravenous use only. The powder must first be reconstituted in the vial using 5 ml water for injection. Dissolution must be complete before the solution is withdrawn. The reconstituted solution is then further diluted with 100 ml of calcium-free infusion solution (0,9 % sodium chloride solution or 5 % glucose solution). If refrigerated, the solution must be allowed to reach room temperature before administration.

If an 8 mg dose is required (retreatment), two vials are each to be reconstituted with 5 ml water for injection as described above and the resulting 10 ml reconstituted solution further diluted with 100 ml 0,9 % sodium chloride solution or 5 % glucose solution.

Incompatibilities:

Glass bottles, as well as several types of infusion bags and infusion lines made from polyvinyl-chloride, polyethylene and polypropylene (prefilled with 0,9 %

sodium chloride solution or 5 % glucose solution), exhibit no incompatibility with **ZOMEDRON**.

To avoid potential incompatibilities, **ZOMEDRON** reconstituted solution is to be diluted with 0,9 % sodium chloride solution or 5 % glucose solution.

ZOMEDRON reconstituted solution must not be mixed with calcium-containing solutions, such as Ringer's solution.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects:

The following side-effects may occur with the use of **ZOMEDRON**:

Blood and lymphatic system disorders:

Frequent: Thrombocytopenia, anaemia, pancytopenia.

The following side-effects have been reported and frequencies are unknown:

Leucopenia.

Immune system disorders:

Frequent: Hypersensitivity reaction, angioneurotic oedema.

Psychiatric disorders:

Frequent: Anxiety, sleep disturbance.

The following side-effects have been reported and frequencies are unknown:

Confusion.

Nervous system disorders:

Frequent: Headache, dizziness, paraesthesia, hypoaesthesia.

Less frequent: Taste disturbance.

The following side-effects have been reported and frequencies are unknown:

Hyperaesthesia, tremor.

Eye disorders:

The following side-effects have been reported and frequencies are unknown:

Conjunctivitis, blurred vision.

Cardiovascular disorders:

Less frequent: Bradycardia.

Respiratory, thoracic and mediastinal disorders:

Frequent: Dyspnoea, cough.

The following side-effects have been reported and frequencies are unknown:

Bronchoconstriction in acetylsalicylic acid-sensitive asthmatic patients.

Gastrointestinal disorders:

Frequent: Nausea, vomiting, anorexia, diarrhoea, abdominal pain, constipation, dry mouth.

The following side-effects have been reported and frequencies are unknown:

Dyspepsia, stomatitis.

Skin and subcutaneous tissue disorders:

Frequent: Increased sweating, rash (including erythematous and macular rash).

Less frequent: Pruritus.

Musculoskeletal, connective tissue and bone:

Frequent: Bone pain, myalgia, arthralgia, muscle cramps.

Renal and urinary disorders:

Frequent: Painful or difficult urination, haematuria.

The following side-effects have been reported and frequencies are unknown:

Renal impairment, acute renal failure, proteinuria.

General disorders and administration site conditions

Frequent: Fever, flu-like syndrome (including fatigue, rigors, malaise and flushing), asthenia, chest pain.

The following side-effects have been reported and frequencies are unknown:

Peripheral oedema, injection site reactions (including pain, irritation, swelling, induration), weight increase.

Laboratory abnormalities:

Frequent: Hypophosphataemia, hypocalcaemia, hypomagnesaemia, hypokalaemia.

The following side-effects have been reported and frequencies are unknown:

Increased blood creatinine and blood urea, hyperkalaemia, hypernatraemia.

Special Precautions:

Effects on ability to drive and use machines:

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There is no documented evidence of acute intoxication with **ZOMEDRON**. 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.

IDENTIFICATION:

Lyophilised powder: White to off white powder/cake.

Reconstituted solution: Clear, colourless solution.

PRESENTATION:

Packed in a carton containing a 10 ml, tubular, transparent, clear glass vial sealed by an aluminium and dark red plastic flip-off seal and grey coloured bromobutyl slotted rubber stopper.

STORAGE INSTRUCTIONS:

Store at or below 25 °C. Protect from light.

The vial must not be removed from the outer carton until required for use.

STORE THIS MEDICINE OUT OF REACH OF CHILDREN.

After aseptic reconstitution and dilution, it is preferable to use the reconstituted and diluted product immediately. If not used immediately, the total time between reconstitution, dilution, storage in a refrigerator at 2 to 8 °C and end of administration must not exceed 24 hours.

REGISTRATION NUMBER:

To be allocated.

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

CIPLA MEDPRO (PTY) LTD.

Rosen Heights

Pasita Street

Rosen Park

Bellville

7530