Proposed Package Insert

ZOCLASTA 5 mg/100 mℓ SOLUTION FOR INFUSION

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

ZOCLASTA 5 mg/100 ml solution for infusion.

COMPOSITION:

100 ml solution contains 5 mg zoledronic acid.

Excipients:

Mannitol, sodium citrate, water for injection.

PHARMACOLOGICAL CLASSIFICATION:

A 34 Other.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Zoledronic acid belongs to the class of nitrogen-containing bisphosphonates. It acts primarily on bone and inhibits osteoclast-mediated bone resorption. Bisphosphonates have a selective action on bone primarily due to their high affinity for mineralised bone. Intravenously administered zoledronic acid is distributed to bone and localises preferentially at sites of high bone turnover. In the osteoclast, the main molecular target for zoledronic acid is the enzyme farnesyl pyrophosphate (FPP) synthase, but this does not exclude other mechanisms. The high binding affinity of zoledronic acid for the active site of FPP synthase and its strong binding affinity to bone mineral result in the relatively long duration of action of zoledronic acid.

Zoledronic acid treatment reduced the rate of bone turnover from elevated post-menopausal levels with the nadir for resorption markers observed at 7 days and for formation markers at 12 weeks. Thereafter bone markers stabilised within the pre-menopausal range. No progressive reduction in bone turnover markers occurred with repeated annual dosing.

Pharmacokinetic properties:

After initiation of intravenous administration of zoledronic acid, the plasma concentration of the active substance increases, and peak concentrations are reached at the end of the infusion period. This is 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 levels.

Elimination of intravenously administered zoledronic acid is by a triphasic process: rapid biphasic disappearance from the systemic circulation, with half lives of $t_{1/2\alpha}$ 0,24 and $t_{1/2\beta}$ 1,87 hours, followed by a long elimination phase with a terminal elimination half-life of $t_{1/2\gamma}$ 146 hours.

There is no accumulation of the active substance in plasma after multiple doses given every 28 days. The early disposition phases (alpha and beta, with $t_{1/2}$ values above) presumably represent uptake into bone and excretion via the kidneys.

Zoledronic acid is not metabolised and undergoes excretion 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 or body weight. Increase of the infusion time from 5 minutes to 15 minutes causes a 30 % decrease in zoledronic acid concentration at the end of the infusion, however, there is no effect on the area under the plasma concentration versus time curve.

Special populations

The renal clearance of zoledronic acid is correlated with creatinine clearance and suggests that dose adjustments of zoledronic acid in mild (Cl_{cr} = 50 to 80 ml/min) and moderate (Cl_{cr} = 30 to 50 ml/min) renal impairment are not necessary. Hence no dose adjustment is necessary in patients with creatinine clearance ≥ 35 ml/min.

In patients with creatinine clearance < 35 ml/min, use of **ZOCLASTA** is not recommended due to limited clinical safety data in such patients (see WARNINGS AND SPECIAL PRECAUTIONS).

INDICATIONS:

- Treatment of osteoporosis in postmenopausal women to reduce the incidence of hip, vertebral and non-vertebral fractures and to increase bone mineral density
- In patients with a recent low trauma hip fracture, **ZOCLASTA** reduces the incidence of new clinical fractures
- Treatment of osteoporosis in men
- Treatment of glucocorticoid-induced osteoporosis
- Treatment of Paget's disease of the bone.

CONTRAINDICATIONS:

- Hypersensitivity to the active substance, any bisphosphonates or any of the excipients of **ZOCLASTA**
- Hypocalcaemia (see WARNINGS AND SPECIAL PRECAUTIONS)
- Pregnancy and lactation (see PREGNANCY AND LACTATION)
- Severe renal function impairment (creatinine clearance < 35 mℓ/min)
- Patients treated with another bisphosphonate should not receive **ZOCLASTA.**
- **ZOCLASTA** is contraindicated for use in children and adolescents below 18 years of age due to lack of data on safety and efficacy.

WARNINGS AND SPECIAL PRECAUTIONS:

Renal dysfunction

Treatment with intravenous bisphosphonates, including **ZOCLASTA**, has been associated with renal impairment manifested as deterioration in renal function (i.e. increased serum creatinine) and in rare cases acute renal failure. Following the administration of **ZOCLASTA** renal dysfunction has been observed especially in patients with pre-existing renal impairment or additional risk factors including oncology patients on chemotherapy, concomitant use of nephrotoxic medicines, concomitant diuretic therapy (see INTERACTIONS) and severe dehydration. Renal failure requiring dialysis has occurred in patients with underlying renal impairment. The majority of these patients received a 4 mg dose every 3 to 4 weeks, but it has been observed in patients following a single administration.

The following precautions should be taken into account to minimise the risk of adverse renal reactions:

- **ZOCLASTA** should not be used in patients with severe renal impairment (creatinine clearance < 35 mℓ/min) due to limited clinical safety data in such patients (see Pharmacokinetic properties and CONTRAINDICATIONS). **ZOCLASTA** should be used with caution in patients concomitantly using other medicines that could impact renal function (see INTERACTIONS).
- Serum creatinine should be measured before each **ZOCLASTA** dose. Transient increase in serum creatinine may be greater in patients with underlying impaired renal function and hence interim monitoring of serum creatinine should be considered in at-risk patients.
- Patients, especially the elderly and those receiving diuretic therapy, should be appropriately hydrated prior to administration of **ZOCLASTA**.
- A single dose of **ZOCLASTA** should not exceed 5 mg and the duration of infusion should not be less than 15 minutes (see DOSAGE AND DIRECTIONS FOR USE).

Hypocalcaemia

Pre-existing hypocalcaemia must be treated by adequate intake of calcium and vitamin D before initiating therapy with **ZOCLASTA** (see CONTRAINDICATIONS). Other disturbances of mineral metabolism such as diminished parathyroid reserve, thyroid surgery, parathyroid surgery and intestinal calcium malabsorption should also be effectively treated prior to commencing therapy

with **ZOCLASTA**. Medical practitioners should consider clinical monitoring for these patients.

Calcium and vitamin D supplementation

Adequate calcium and vitamin D supplementation is recommended in men and women undergoing therapy with **ZOCLASTA** for the treatment of osteoporosis if dietary intake is inadequate. Supplementation with calcium and vitamin D is also recommended in patients treated to prevent clinical fractures following a hip fracture.

Treatment of Paget's disease of the bone

Elevated bone turnover is a characteristic of Paget's disease of the bone. Zoledronic acid has a rapid onset of effect on bone turnover and as a result transient hypocalcaemia, sometimes symptomatic, may develop and is usually maximal within the first 10 days following intravenous infusion of **ZOCLASTA** (see SIDE EFFECTS). Adequate vitamin D intake is recommended in association with **ZOCLASTA** administration. In addition, it is strongly recommended that adequate supplementation with calcium corresponding to at least 500 mg elemental calcium twice a day is ensured in patients with Paget's disease for at least 10 days following **ZOCLASTA** administration. Patients should be informed about the symptoms of hypocalcaemia and medical practitioners should consider clinical monitoring of patients at risk.

Musculoskeletal pain

Severe and occasionally incapacitating bone, joint and /or muscle pain have been reported in patients taking **ZOCLASTA**.

Atypical fractures of the femur

Atypical, low energy fractures of the subtrochanteric and proximal femoral shaft have been reported with long-term use (usually longer than 3 years) in bisphosphonate-treated patients. 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. Bisphosphonate treatment should be stopped in patients with stress fractures and they should receive appropriate orthopaedic care.

Osteonecrosis of the jaw

Osteonecrosis of the jaw generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimens including primarily intravenous administered bisphosphonates. Many of these were receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates, such as **ZOCLASTA**. A dental examination with appropriate preventative dentistry should be considered prior to treatment with bisphosphonates, such as **ZOCLASTA** in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene). While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, such as **ZOCLASTA**, 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. Clinical judgment of the treating doctor should guide the management plan of each patient based on an individual benefit/risk assessment.

Effects on ability to drive and use machines

Drowsiness, dizziness, and somnolence have been reported in patients receiving **ZOCLASTA**. Patients should exercise caution before driving and using machinery until they are certain that **ZOCLASTA** does not adversely affect performance.

INTERACTIONS:

ZOCLASTA does not undergo systemic metabolism and does not affect cytochrome P450 enzymes *in vitro*.

The plasma protein binding of **ZOCLASTA** is low (approximately 43 - 55 % bound) and hence interactions due to displacement of highly protein-bound medicines are unlikely.

ZOCLASTA is excreted via the kidneys.

Caution should be exercised when **ZOCLASTA** is administered concomitantly with medicines that can significantly impact renal function, including aminoglycosides or diuretics that may cause dehydration. There may also be additive hypocalcaemic effects with aminoglycosides.

An increase in the systemic exposure of concomitantly administered medicines which are primarily excreted via the kidneys may occur in renally impaired patients.

PREGNANCY AND LACTATION:

ZOCLASTA is contraindicated during pregnancy and in breastfeeding women (see CONTRAINDICATIONS).

DOSAGE AND DIRECTIONS FOR USE:

General:

The incidence of post-dose symptoms occurring within the first three days after administration of **ZOCLASTA** can be reduced with the administration of paracetamol or ibuprofen shortly following **ZOCLASTA** administration.

Prior to administration of **ZOCLASTA**, patients must be appropriately hydrated. This is especially important in the elderly and for patients receiving diuretic therapy (see WARNINGS AND SPECIAL PRECAUTIONS).

Treatment of postmenopausal osteoporosis:

The recommended dose is a single intravenous infusion of 5 mg **ZOCLASTA** administered once a year.

Adequate supplemental calcium and vitamin D intake is important in women with osteoporosis if dietary intake is inadequate (see WARNINGS AND SPECIAL PRECAUTIONS).

Treatment of osteoporosis in men:

The recommended dose is a single intravenous infusion of 5 mg **ZOCLASTA** administered once a year.

Adequate supplemental calcium and vitamin D intake is important in men with osteoporosis if dietary intake is inadequate (see WARNINGS AND SPECIAL PRECAUTIONS).

Treatment of glucocorticoid-induced osteoporosis:

The recommended dose is a single intravenous infusion of 5 mg **ZOCLASTA** administered once a year.

Adequate supplemental calcium and vitamin D intake is important in patients with osteoporosis if dietary intake is inadequate (see WARNINGS AND SPECIAL PRECAUTIONS).

Treatment of Paget's disease of bone:

ZOCLASTA should be prescribed only by medical practitioner with experience in treatment of Paget's disease of the bone.

The recommended dose is one intravenous infusion of 5 mg zoledronic acid (anhydrous) in 100 mℓ aqueous solution administered intravenously via a vented infusion line, given at a constant infusion rate.

Re-treatment of Paget's disease:

Specific re-treatment data are not available.

After a single treatment with **ZOCLASTA** in Paget's disease an extended remission period is observed in responding patients (see PHARMACODYNAMIC PROPERTIES). However, re-treatment with **ZOCLASTA** may be considered in patients who have relapsed, based on increases in serum alkaline phosphatase, in patients who failed to achieve normalisation of serum alkaline phosphatase, or in patients with symptoms, as dictated by medical practice 12 months after the initial dose.

In patients with Paget's disease, it is recommended that adequate vitamin D intake occurs during **ZOCLASTA** treatment. Further, adequate supplementation with calcium corresponding to at least 500 mg elemental calcium twice a day is strongly recommended for at least 10 days following **ZOCLASTA** administration (see WARNINGS AND SPECIAL PRECAUTIONS).

Patients with renal impairment:

There is limited clinical safety data in patients with creatinine clearance < 35 ml/min and hence the use of **ZOCLASTA** in such patients is contraindicated (see CONTRAINDICATIONS)

No dose adjustment is necessary in patients with creatinine clearance ≥ 35 ml/min.

Patients with hepatic impairment:

No dose adjustment is required.

Elderly (≥ 65 years):

No dose adjustment is necessary since bioavailability, distribution and elimination were similar in elderly and younger patients.

Instructions for use and handling

ZOCLASTA (5 mg in 100 mℓ ready to infuse solution) is administered intravenously via a vented infusion line, given at a constant infusion rate. The infusion time must not be less than 15 minutes. **ZOCLASTA** must not be mixed or given intravenously with any other medication and must be given through a separate vented infusion line at a constant infusion rate. If refrigerated, allow the refrigerated solution to reach room temperature before administration. Aseptic techniques must be followed during the preparation of the infusion.

For single use only. Any unused solution should be discarded. Only clear solution free from particles and discolouration should be utilised.

Pharmaceutical incompatibilities

ZOCLASTA solution for infusion must not be allowed to come into contact with any calcium-containing solutions.

SIDE EFFECTS

ZOCLASTA has been frequently associated with the following post-dose symptoms: fever, myalgia, flu-like symptoms, arthralgia and headache. The majority of these symptoms occur within the first 3 days following administration of **ZOCLASTA**. The majority of these symptoms were mild to moderate in nature and resolved within 3 days of the event onset. With subsequent annual doses of **ZOCLASTA**, the incidence of these symptoms decreased.

The incidence of post-dose symptoms occurring within the first 3 days after administration of **ZOCLASTA**, can be reduced by approximately 50 % with the administration of paracetamol or ibuprofen shortly following **ZOCLASTA** administration as needed.

The following side effects have been reported with **ZOCLASTA:**

Immune system disorders

Frequency unknown: Hypersensitivity, angioedema, anaphylactic reaction/ shock

Infections and Infestations

Less frequent: Influenza, nasopharyngitis

Blood and lymphatic system disorders

Less frequent: Anaemia

Metabolism and nutrition disorders

Less frequent: Anorexia, decreased appetite

Psychiatric disorders

Less frequent: Insomnia

Nervous system disorders

Frequent: Headache, dizziness

Less frequent: Lethargy, paraesthesia, somnolence, tremor, syncope

Eye disorders

Less frequent: Conjunctivitis, eye pain, uveitis, episcleritis, iritis

Ear and labyrinth disorders

Less frequent: Vertigo

Cardiac disorders

Less frequent: Atrial fibrillation

Vascular disorders

Less frequent: Hypertension, flushing

Frequency unknown: Hypotension

Respiratory, thoracic and mediastinal disorders

Less frequent: Cough, dyspnoea

Gastrointestinal disorders

Frequent: Nausea, vomiting, diarrhoea

Less frequent: Dyspepsia, abdominal pain upper, abdominal pain, gastroesophageal reflux disease, constipation, dry mouth, oesophagitis

Skin and subcutaneous tissue disorders

Less frequent: Rash, hyperhidrosis, pruritus, erythema

Musculoskeletal, connective tissue and bone disorders

Frequent: Myalgia, arthralgia, bone pain, back pain, pain in extremity

Less frequent: Neck pain, musculoskeletal stiffness, joint swelling, muscle spasms, shoulder pain, musculoskeletal pain, joint stiffness, arthritis, muscular weakness

Frequency unknown: Osteonecrosis of the jaw. Cases of osteonecrosis (primarily of the jaw) have been reported predominantly in cancer patients treated with **ZOCLASTA** (see WARNINGS AND SPECIAL PRECAUTIONS).

Renal and urinary disorders

Less frequent: Increased blood creatinine, pollakuria, proteinuria, acute renal failure

General disorders and administrative site conditions

Frequent: Fever, flu-like symptoms, chills, fatigue, asthenia, pain, malaise

Less frequent: Peripheral oedema, thirst, acute phase reaction, non-cardiac chest pain

Frequency unknown: Thrombophlebitis, dehydration secondary to post-dose symptoms such as fever, vomiting and diarrhoea

Investigations:

Symptomatic hypocalcaemia was observed less frequently in patients being treated with zoledronic acid for Paget's disease (see WARNINGS AND SPECIAL PRECAUTIONS).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms: Exacerbation of side effects.

Treatment

Patients who have received doses higher than recommended should be carefully monitored. In cases of over dosage leading to clinically significant hypocalcaemia, reversal may be achieved with supplemental oral calcium and/ or an infusion of calcium gluconate (see WARNINGS AND SPECIAL PRECAUTIONS).

IDENTIFICATION:

ZOCLASTA is a sterile, clear and colourless solution. The solution is free from particles.

PRESENTATION:

ZOCLASTA 5 mg/100 mℓ solution for infusion is supplied in a clear 100 mℓ silicone dioxide inner coated glass vial capped with a bromobutyl rubber stopper and sealed with an aluminium polypropylene flip off seal. **ZOCLASTA** is supplied in packs containing one bottle or multipacks comprising three or six packs, each containing one bottle and a vented infusion set. Not all pack sizes may be marketed.

STORAGE INSTRUCTIONS:

Store **ZOCLASTA** at or below 25 °C.

Store in the original packaging until a doctor or nurse administers **ZOCLASTA**.

The **ZOCLASTA** vial is for single use only. **ZOCLASTA** should be used immediately and the entire volume in the bottle should be administered.

The product does not contain preservatives and hence for microbiological reasons, the ready to use product should be used immediately after opening and the entire content should be administered. However, after opening, the solution is chemically and physically stable for 24 hours when kept either at room temperature (25 °C) or in a refrigerator (2 to 8 °C).

Do not freeze.

KEEP THIS MEDICINE OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBER

49/34/1081

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

Camox Pharmaceuticals (Pty) Ltd.

52 Mineral Crescent

Crown Ext 3, Johannesburg

2092, South Africa

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