SCHEDULING STATUS

S4

1. **NAME OF THE MEDICINE:**

   BONAZOLL 5 mg/100 mL solution for infusion

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION:**

   BONAZOLL 5 mg/100 mL solution for infusion

   Each vial contains 5,33 mg of zoledronic acid monohydrate equivalent to 5 mg zoledronic acid anhydrous.

   Contains: Mannitol 4,950 g/100 mL

   Contains sodium: Sodium citrate 30 mg/100 mL.

   For the full list of excipients, see **section 6.1.**

3. **PHARMACEUTICAL FORM:**

   BONAZOLL 5 mg/100 mL solution for infusion is a clear, colourless, sterile solution.

4. **CLINICAL PARTICULARS:**

   4.1 Therapeutic 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, **BONAZOLL 5** reduces the incidence of new clinical fractures.
   - Treatment of osteoporosis in men.

- Treatment of glucocorticoid-induced osteoporosis. Treatment of Paget's disease of bone.

4.2 Posology and method of administration

Posology

The incidence of post-dose symptoms occurring within the first three days after administration of **BONAZOLL 5** can be reduced with the administration of paracetamol or ibuprofen shortly following **BONAZOLL 5** administration.

Patients must be appropriately hydrated prior to administration of zoledronic acid. This is especially important for the elderly (≥ 65 years) and for patients receiving diuretic therapy (see section 4.4).

Treatment of postmenopausal osteoporosis, osteoporosis in men and glucocorticoid- induced osteoporosis:

The recommended dose is a single intravenous infusion of 5 mg infusion of **BONAZOLL 5** administered once a year. Adequate supplemental calcium and vitamin D intake is important in patients with osteoporosis if dietary intake is inadequate.

Treatment of Paget's disease of bone:

For the treatment of Paget's disease **BONAZOLL 5** should be prescribed only by medical practitioners with experience in treatment of Paget's disease of the bone.

The recommended dose is one intravenous infusion of 5 mg **BONAZOLL 5** (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 **BONAZOLL 5** in Paget's disease, an extended remission period is observed in responding patients (see section 5.1). However, re-treatment with **BONAZOLL 5** 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, adequate vitamin D intake is recommended in association with **BONAZOLL 5** administration. In addition, it is strongly advised that adequate supplemental calcium corresponding to at least 500 mg elemental calcium twice daily is ensured in patients with Paget's disease for at least 10 days following **BONAZOLL 5** administration (see section 4.4).

Special populations

Elderly population

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

Renal Impairment

The use of **BONAZOLL 5** in patients with creatinine clearance < 35 mL /min is not recommended due to limited clinical safety data in such patients (see sections 4.3 and 4.4). No dose adjustment is necessary in patients with creatinine clearance ≥ 35 mL /min.

Hepatic Impairment

No dose adjustment is required (see section 5.2).

Paediatric population

BONAZOLL 5 is not recommended for use in children and adolescents below 18 years of age due to lack of data on safety and efficacy.

Method of administration

Intravenous use.

BONAZOLL 5 (5 mg in 100 mL ready-to-infuse solution) is administered via a vented infusion line and given at a constant infusion rate. The infusion time must not be less than 15 minutes.

For further information on the handling of zoledronic acid solution for infusion, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to any bisphosphonates.
- Hypocalcaemia (see section 4.4)
- Pregnancy and lactation (see section 4.6).
- Severe impairment of renal function (creatinine clearance of < 35 mL /min): the safety and
- efficacy in patients with severe renal impairment have not been established.

4.4 Special warnings and precautions for use

Renal function

The use of **BONAZOLL 5** in patients with severe renal impairment (creatinine clearance < 35 mL/min) is contraindicated due to an increased risk of renal failure in this population.

Renal impairment has been observed following the administration of zoledronic acid (see section 4.8), especially in patients with pre-existing renal dysfunction or other risks including advanced age, concomitant nephrotoxic medicines, concomitant diuretic therapy (see section 4.5), or dehydration occurring after zoledronic acid administration. Renal impairment has been observed in patients after a single administration. Renal failure requiring dialysis or with a fatal outcome has rarely occurred in patients with underlying renal impairment or with any of the risk factors described above.

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

- Patients should have serum creatinine measured before receiving each **BONAZOLL 5** dose.
- Creatinine clearance should be calculated based on actual body weight using the Cockcroft-Gault formula before each **BONAZOLL 5** dose.
- Transient increase in serum creatinine may be greater in patients with underlying impaired renal function.
- Monitoring of serum creatinine should be considered in at-risk patients
- **BONAZOLL 5** should be used with caution when concomitantly used with other medicines that could impact renal function (see section 4.5)

- Patients, especially elderly patients and those receiving diuretic therapy, should be appropriately hydrated prior to administration of zoledronic acid
- A single dose of **BONAZOLL 5** should not exceed 5 mg and the duration of infusion should be at least 15 minutes (see section 4.2).

Hypocalcaemia

Pre-existing hypocalcaemia must be treated by adequate intake of calcium and vitamin D before initiating therapy with **BONAZOLL 5** (see section 4.3). Other disturbances of mineral metabolism must also be effectively treated (e.g. diminished parathyroid reserve, intestinal calcium malabsorption). Medical Practitioners should consider clinical monitoring for these patients.

Elevated bone turnover is a characteristic of Paget's disease of the bone. Due to the rapid onset of effect of zoledronic acid as in **BONAZOLL 5** on bone turnover, transient hypocalcaemia, sometimes symptomatic, may develop and is usually maximal within the first 10 days after infusion of zoledronic acid (see section 4.8). Adequate calcium and vitamin D intake are recommended in association with **BONAZOLL 5** administration, in patients with osteoporosis if dietary intake is inadequate and to prevent clinical fractures after a hip fracture. In addition, in patients with Paget's disease, it is strongly advised that adequate supplemental calcium corresponding to at least 500 mg elemental calcium twice daily is ensured for at least 10 days following **BONAZOLL 5** administration (see section 4.2). Patients should be informed about symptoms of hypocalcaemia and receive adequate clinical monitoring during the period of risk. Measurement of serum

calcium before infusion of **BONAZOLL 5** is recommended for patients with Paget´s disease.

Musculoskeletal pain

Severe and occasionally incapacitating bone, joint and/or muscle pain have been infrequently reported in patients taking bisphosphonates, including zoledronic acid (see section 4.8).

Osteonecrosis of the jaw (ONJ)

Osteonecrosis of the jaw has been reported in the post-marketing setting in patients receiving zoledronic acid as in **BONAZOLL 5** for osteoporosis (see section 4.8). 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. A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with **BONAZOLL 5** in patients with concomitant risk factors.

The following should be considered when evaluating a patient's risk of developing ONJ:

- Potency of the medicine that inhibits bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy.
- Cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking.
- Concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck.

- Poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures, e.g. tooth extractions.

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, non-healing of sores or discharge during treatment with zoledronic acid. While on treatment, invasive dental procedures should be performed with caution and avoided in close proximity to **BONAZOLL 5** treatment. 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 **BONAZOLL 5** 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.

Atypical fractures of the femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate 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 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. Discontinuation of bisphosphonate 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.

During bisphosphonate 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.

Acute phase reactions

Acute phase reactions (APRs) or post-dose symptoms such as fever, myalgia, flu-like symptoms, arthralgia and headache have been observed, the majority of which occurred within three days following zoledronic acid administration.

APRs may sometimes be serious or prolonged in duration. The incidence of post-dose symptoms can be reduced with the administration of paracetamol or ibuprofen shortly following **BONAZOLL 5** administration. It is also advisable to postpone treatment if the patient is clinically unstable due to an acute medical condition and an APR could be problematic (see section 4.8).

General

Other medicines containing zoledronic acid as an active substance are available for oncology indications. Patients being treated with **BONAZOLL 5** solution for infusion should not be treated with such medicines or any other bisphosphonate concomitantly, since the combined effects of these medicines are unknown.

BONAZOLL 5 contains:

Sodium: This medicine contains less than 1 mmol sodium (23 mg) per 100 ml vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies with other medicines have been performed.

Zoledronic acid is not systemically metabolized and does not affect human cytochrome P450 enzymes in vitro (see section 5.2). Zoledronic acid is not highly bound to plasma proteins (approximately 43-55 % bound) and interactions resulting from displacement of highly protein-bound medicines are therefore unlikely.

Zoledronic acid is eliminated by renal excretion. Caution is indicated when **BONAZOLL 5** is administered in conjunction with medicines that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration) (see section 4.4).

In patients with renal impairment, the systemic exposure to concomitant medicines that are primarily excreted via the kidney may increase.

BONAZOLL 5 solution for infusion must not be allowed to come into contact with any calcium containing solutions.

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential

BONAZOLL 5 is not recommended in women of childbearing potential**.**

Pregnancy

BONAZOLL 5 is contraindicated during pregnancy (see section 4.3). There are no adequate data on the use of zoledronic acid in pregnant women. Studies in animals with zoledronic acid have shown reproductive toxicological effects including malformations. The potential risk for humans is unknown.

Breastfeeding

BONAZOLL 5 is contraindicated during breast-feeding (see section 4.3). It is unknown whether **BONAZOLL 5** is excreted into human milk.

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 related to the compound's inhibition of skeletal calcium mobilisation, resulting in periparturient hypocalcaemia, a bisphosphonate class effect, dystocia and early termination of the study. Thus, these results precluded determining a definitive effect of **BONAZOLL 5** on fertility in humans.

4.7 Effects on the ability to drive and use machines

Adverse reactions, such as dizziness and somnolence, may affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported side effects within 3 days of zoledronic acid dosing were pyrexia, myalgia, influenza-like illness, arthralgia and headache, (see "acute phase reactions" below and section 4.4.)

Adverse Effects

Infections and infestations

Less frequent: influenza, nasopharyngitis

Blood and lymphatic system disorders

*Less frequent**:** anaemia*

Immune system disorders

Frequency unknown: hypersensitivity reactions including rare cases of bronchospasm, urticaria and angioedema, and very rare cases of anaphylactic reaction/shock.

Metabolism and nutrition disorders

Frequent: hypocalcaemia (common in Paget's disease)

Less frequent: decreased appetite, hypophosphataemia

Psychiatric disorders

Less frequent: insomnia

Nervous system disorders

Frequent: headache, dizziness

Less frequent: lethargy, paraesthesia, somnolence, tremor, syncope, dysgeusia

Eye disorders

Frequent: ocular hyperaemia

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

Frequency unknown: scleritis and parophthalmia

Ear and labyrinth disorders

Less frequent: Vertigo

Cardiac disorders

Frequent: atrial fibrillation

Less frequent: palpitations

Vascular disorders

Less frequent: hypertension, flushing

Frequency unknown: hypotension (some of the patients had underlying risk factors)

Respiratory, thoracic and mediastinal disorders

Less frequent: dyspnoea, cough

Gastrointestinal disorders

Frequent: nausea, vomiting, diarrhoea

Less frequent: dyspepsia, abdominal pain upper, abdominal pain, gastro-oesophageal reflux disease, constipation, dry mouth, oesophagitis, toothache, gastritis (observed in patients taking concomitant glucocorticoids)

Skin and subcutaneous tissue disorders

Less Frequent: rash, hyperhidrosis, pruritus, erythema

Musculoskeletal and connective tissue disorders

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

Less frequent: neck pain, musculoskeletal stiffness, joint swelling, shoulder pain, muscle spasms, musculoskeletal chest pain, musculoskeletal pain, joint stiffness, arthritis, muscular weakness, osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction).

Frequency unknown: osteonecrosis of the jaw (see sections 4.4 and 4.8 Class effects), atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction).

Renal and urinary disorders

Less frequent: blood creatinine increased, pollakiuria, proteinuria

Frequency unknown: renal impairment. Rare cases of renal failure requiring dialysis and rare cases with a fatal outcome have been reported in patients with pre-existing renal dysfunction or other risk factors such as advanced age, concomitant nephrotoxic medicines, concomitant diuretic therapy, or dehydration in the post infusion period (see sections 4.4 and 4.8 class effects)

General disorders and administration site conditions

Frequent: pyrexia, influenza-like illness, chills, fatigue, asthenia, pain, malaise, infusion site reaction

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

Frequency unknown: dehydration secondary to acute phase reactions (post-dose symptoms such as pyrexia, vomiting and diarrhoea)

Investigations

Frequent: C-reactive protein increased

Less frequent: blood calcium decreased

Class effects:

Description of selected adverse reactions

Renal impairment

Zoledronic acid has been associated with renal impairment manifested as deterioration in renal function (i.e. increased serum creatinine) and in rare cases acute renal failure. Renal impairment has been observed following the administration of zoledronic acid, especially in patients with pre-existing renal dysfunction or additional risk factors (e.g. advanced age, oncology patients with chemotherapy, concomitant nephrotoxic medicines, concomitant diuretic therapy, severe dehydration), the majority of whom received 4 mg dose every 3-4 weeks, but it has been observed in patients after a single administration.

In clinical trials in osteoporosis, the change in creatinine clearance (measured annually prior to dosing) and the incidence of renal failure and impairment was comparable for both the zoledronic acid and placebo treatment groups over three years. There was a transient increase in serum creatinine observed within 10 days in of zoledronic acid-treated and placebo-treated patients.

Hypocalcaemia

In clinical trials in osteoporosis, approximately 0,2 % of patients had notable declines of serum calcium levels (less than 1,87 mmol/L) following zoledronic acid administration. No symptomatic cases of hypocalcaemia were observed.

In the Paget's disease trials, symptomatic hypocalcaemia was observed in approximately 1 % of patients, in all of whom it resolved.

Based on laboratory assessment, transient asymptomatic calcium levels below the normal reference range (less than 2,10 mmol/L) occurred in 2,3 % of zoledronic acid-treated patients in a large clinical trial compared to 21 % of zoledronic acid-treated patients in the Paget's disease trials. The frequency of hypocalcaemia was much lower following subsequent infusions.

All patients received adequate supplementation with vitamin D and calcium in the post-menopausal osteoporosis trial, the prevention of clinical fractures after hip fracture trial, and the Paget's disease trials (see also section 4.2). In the trial for the prevention of clinical fractures following a recent hip fracture, vitamin D levels were not routinely measured but the majority of patients received a loading dose of vitamin D prior to zoledronic acid administration (see section 4.2).

Local reactions

Local reactions at the infusion site, such as redness, swelling and/or pain, were reported following the administration of zoledronic acid in clinical trials.

Osteonecrosis of the jaw

Cases of osteonecrosis of the jaw have been reported, predominantly in cancer patients treated with medicines that inhibit bone resorption, including zoledronic acid, as in **BONAZOLL 5** (see section 4.4). Cases of ONJ have been reported in the post-marketing setting for zoledronic acid.

Acute phase reactions

In a study on the treatment of post-menopausal osteoporosis the most frequently reported side effects were: fever, myalgia, flu-like symptoms, arthralgia and headache, the majority of which occurred within the first 3 days following

zoledronic acid administration. The majority of these symptoms were mild to moderate in nature and resolved within 3 days of the event onset. The incidence of these symptoms decreased with subsequent annual doses of zoledronic acid. The percentage of patients who experienced adverse reactions was lower where prophylaxis against adverse reactions was used (see section 4.4).

Reporting side effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of benefit/risk balance of the medicine. Health care 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: hppts://www.sahpra.or.za/Publications/Index/8

4.9 Overdose

Clinical experience with acute overdose is limited. Patients who have received doses higher than those recommended should be carefully monitored. In the event of overdose leading to clinically significant hypocalcaemia, reversal may be achieved with supplemental oral calcium and/or an intravenous infusion of calcium gluconate.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacological classification: A 34 Other

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

Mechanism of action:

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

Pharmacodynamic effects:

Osteoporosis:

Zoledronic acid treatment reduced the rate of bone turnover from elevated postmenopausal levels with the nadir for resorption markers observed at 7 days, and for formation markers at 12 weeks. Thereafter bone markers stabilized within the premenopausal range. There was no progressive reduction of bone turnover markers with repeated annual dosing. In long-term animal studies, zoledronic acid inhibits bone resorption without adversely affecting bone formation, mineralisation or the mechanical properties of bone. Continuing bone remodelling was observed in bone samples from all animals treated with clinically relevant doses of

zoledronic acid. There was no evidence of a mineralising defect, no aberrant accumulation of osteoid, and no woven bone in treated animals.

5.2 Pharmacokinetic properties

Single and multiple 5 and 15-minute infusions of 2, 4, 8 and 16 mg zoledronic acid yielded the following pharmacokinetic data, which were found to be dose independent.

Distribution

After initiation of the zoledronic acid infusion, plasma concentrations of the active substance increased rapidly, 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 levels.

Elimination

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 the active substance in plasma after multiple doses given every 28 days. The early disposition phases (α and β, with $t_{½}$ values above) presumably represent rapid uptake into bone and excretion via the kidneys.

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. This uptake into bone is common for all bisphosphonates and is presumably a consequence of the structural analogy to pyrophosphate. The retention time of zoledronic acid in bones is very long. 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/hour, independent of dose, and unaffected by gender, age, race or body weight. The inter- and intra-subject variation for plasma clearance of zoledronic acid was shown to be 36 % and 34 %, respectively. 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.

Pharmacokinetic/pharmacodynamic relationships

No interaction studies with other medicines have been performed with zoledronic acid. Since zoledronic acid is not metabolised in humans and the substance was found to have little or no capacity as a direct-acting and/or irreversible metabolism-dependent inhibitor of P450 enzymes, zoledronic acid is unlikely to reduce the metabolic clearance of substances which are metabolised via the cytochrome P450 enzyme systems. Zoledronic acid is not highly bound to plasma proteins (approximately 43-55 % bound) and binding is concentration independent. Therefore, interactions resulting from displacement of highly protein-bound medicines are unlikely.

Special populations (see section 4.2)

Renal impairment

The renal clearance of zoledronic acid was correlated with creatinine clearance, renal clearance representing 75 ± 33 % of the creatinine clearance, which showed a mean of 84 ± 29 mL/min (range 22 to 143 mL/min). Small observed increases in $AUC_{(0\text{-}24hr)}$, by about 30 % to 40 % in mild to moderate renal impairment, compared to a patient with normal renal function, and lack of accumulation of medicine with multiple doses irrespective of renal function, suggest that dose adjustments of zoledronic acid in mild (Clcr = 50-80 mL/min) and moderate renal impairment down to a creatinine clearance of 35 mL/min are not necessary. The use of zoledronic acid in patients with severe renal impairment (creatinine clearance < 35 mL/min) is contraindicated due to an increased risk of renal failure in this population.

5.3 Pre-clinical safety data

Mutagenicity and carcinogenic potential

Zoledronic acid was not mutagenic in the mutagenicity tests performed and carcinogenicity testing did not provide any evidence of carcinogenic potential.

6. Pharmaceutical particulars

6.1 List of excipients

Mannitol, sodium citrate.

6.2 Incompatibilities

BONAZOLL 5 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. **BONAZOLL 5** solution for infusion must not be allowed to

come into contact with any calcium containing solutions.

6.3 Shelf life

Before reconstitution: 36 months

After opening the solution: 24 hours at 2 to 8 °C.

6.4 Special precautions for storage

Store at or below 25 °C. Keep product in outer container until required for use.

6.5 Nature and contents of container

A clear type II glass vial capped with a type I bromobutyl rubber stopper and sealed with an aluminum polypropylene flip off seal. The vial is packed into carton boxes along with the patient information Leaflet(s) (PIL).

6.6 Special precautions for disposal and other handling

For single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Only clear solution free from particles and discoloration should be used.

If refrigerated, allow the refrigerated solution to reach room temperature before administration. Aseptic techniques must be followed during the preparation of the infusion.

BONAZOLL 5 (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.

7. Holder of certificate of registration

Innovata Pharmaceuticals

Crownwood Office Park

100 Northern Parkway

Ormonde

Johannesburg

2091

South Africa

8. Registration numbers

A 55/34/0903

9. Date of first authorization/Renewal of the authorization

29 August 2023

10. Date of revision of the text

Date of Leaflet: 29 Aug 2023