PATIENT INFORMATION LEAFLET [1]

SCHEDULING STATUS: S4

ZOLEDRONIC ACID 4 mg/5 ml FRESENIUS

Concentrate for solution for infusion

Zoledronic acid

Sugar free

Read all of this leaflet carefully before you are given ZOLEDRONIC ACID FRESENIUS

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other healthcare provider.
- ZOLEDRONIC ACID FRESENIUS has been prescribed for you personally.

What is in this leaflet

1. What ZOLEDRONIC ACID FRESENIUS is and what it is used for
2. What you need to know before you are given ZOLEDRONIC ACID FRESENIUS
3. How ZOLEDRONIC ACID FRESENIUS is given
4. Possible side effects
5. How to store ZOLEDRONIC ACID FRESENIUS
6. Contents of the pack and other information

[1] The annotated version with SAHPRA's revisions appears in m1.5.5.2

1. What ZOLEDRONIC ACID FRESENIUS is and what it is used for

The active substance in ZOLEDRONIC ACID FRESENIUS is zoledronic acid, which belongs to a group of substances called bisphosphonates. Zoledronic acid works by attaching itself to the bone and slowing down the rate of bone change.

ZOLEDRONIC ACID FRESENIUS is used for:

ZOLEDRONIC ACID FRESENIUS slows progression of skeletal conditions in adult patients when used together with appropriate anticancer therapy in patients with advanced carcinoma (type of cancer) of the breast, prostate, lung and myeloma (bone marrow cancer).

2. What you need to know before you are given ZOLEDRONIC ACID FRESENIUS

Do not use ZOLEDRONIC ACID FRESENIUS if you:

- are hypersensitive (allergic) to zoledronic acid, any other bisphosphonates, or to any of the other ingredients of ZOLEDRONIC ACID FRESENIUS (listed in section 6);
- suffer from severely impaired kidney function;
- are pregnant or breastfeeding (see "**Pregnancy and breastfeeding**").

Warnings and precautions

Special care should be taken with ZOLEDRONIC ACID FRESENIUS

Tell your doctor or healthcare provider:

- if you have or have had a kidney problem;
- if your blood calcium concentration is too high, possibly due to a tumour;

- if you have or have had pain, swelling or numbness of the jaw, a feeling of heaviness in the jaw or loosening of a tooth. See *"Osteonecrosis*" below. Your doctor may recommend a dental examination before you start treatment with ZOLEDRONIC ACID FRESENIUS;
- if you have or have had a heart problem;
- if you have ear infection or trauma. See *"Osteonecrosis*" below;
- if you are having dental treatment or are due to undergo dental surgery. Tell your dentist that you are being treated with ZOLEDRONIC ACID FRESENIUS and inform your doctor about your dental treatment.

Osteonecrosis:

Osteonecrosis of the jaw has been reported (see section 4.8). Osteonecrosis is a severe bone disease.

Patients who are undergoing chemotherapy and/or radiotherapy, who are taking steroids, who are undergoing dental surgery, who do not receive routine dental care, who have gum disease, who are smokers, or who were previously treated with a bisphosphonate (used to treat or prevent bone disorders) may have a higher risk of developing osteonecrosis of the jaw.

While being treated with ZOLEDRONIC ACID FRESENIUS you should maintain good oral hygiene (including regular teeth brushing) and receive routine dental check-ups.

Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, non-healing of sores or discharge, as these could be signs of a condition called osteonecrosis of the jaw.

Osteonecrosis of the **outer ear canal** has also been reported with ZOLEDRONIC ACID FRESENIUS. The risk is higher if you have infection

or trauma or if you take or use corticosteroid and/or cancer medicines. Tell your doctor if you have ear pain or discharge from the ear or have an ear infection during treatment.

Osteonecrosis of other sites, including the **hip and femur** (the upper leg bone) has been reported, mainly in adult cancer patients treated with ZOLEDRONIC ACID FRESENIUS. Tell your doctor if you have hip or bone pain during treatment.

Fracturs of the femur

Femur (the upper leg bone) fractures have been reported in patients treated with bisphosphonates such as ZOLEDRONIC ACID FRESENIUS. Tell your doctor if you have hip or bone pain during treatment.

Hypocalcaemia

Reduced levels of calcium in the blood (hypocalcaemia), sometimes leading to muscle cramps, dry skin, burning sensation, have been reported in patients treated with zoledronic acid as in ZOLEDRONIC ACID FRESENIUS. Irregular heartbeat (cardiac dysrhythmia), seizures, spasm and twitching (tetany) have been reported as secondary to severe hypocalcaemia. In some instances, the hypocalcaemia may be life-threatening. If any of these apply to you, tell your doctor straight away. If you have pre-existing hypocalcaemia, it must be corrected before initiating the first dose of ZOLEDRONIC ACID FRESENIUS. You will be given adequate calcium and vitamin D supplements.

Muscle and bone pain

Severe bone, joint and muscle pain may occur with bisphosphonates such as ZOLEDRONIC ACID FRESENIUS. Tell your doctor if you have trouble with pain.

Patients aged 65 years and over

ZOLEDRONIC ACID FRESENIUS can be given to people aged 65 years and over. There is no evidence to suggest that any extra precautions are needed.

Children and adolescents

ZOLEDRONIC ACID FRESENIUS is not recommended for use in children and adolescents below the age of 18 years.

Other medicines and ZOLEDRONIC ACID FRESENIUS

Always tell your healthcare provider if you are taking any other medicine. (This includes all complementary or traditional medicines.)

- Aminoglycosides (antibiotic medicines used to treat severe infections), calcitonin (a medicine used to treat post-menopausal osteoporosis and hypercalcaemia), loop diuretics (a type of medicine to treat high blood pressure or oedema) or other calcium-lowering medicines, since the combination of these with bisphosphonates such as ZOLEDRONIC ACID FRESENIUS may cause the calcium level in the blood to become too low.
- Anti-angiogenic medicines (used to treat cancer) or corticosteroids (used to treat inflammation), since the combination of these with zoledronic acid as in ZOLEDRONIC ACID FRESENIUS has been associated with an increased risk of osteonecrosis of the jaw (ONJ).
- Thalidomide (a medicine used to treat a certain type of blood cancer involving the bone) or any other medicines which may harm your kidneys.

– Medicines that also contain zoledronic acid used to treat osteoporosis and other non-cancer diseases of the bone, or any other bisphosphonate, since the combined effects of these medicines taken together with zoledronic acid are unknown.

Pregnancy, breastfeeding and fertility

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other healthcare provider for advice:

You should not be given ZOLEDRONIC ACID FRESENIUS if you are pregnant. Tell your doctor if you are or think that you may be pregnant.

You should avoid getting pregnant. There is a possible hazard to your unborn baby if you receive ZOLEDRONIC ACID FRESENIUS, as the foetus may for example have skeletal and other abnormalities. See “Do not use ZOLEDRONIC ACID FRESENIUS”.

You must not be given ZOLEDRONIC ACID FRESENIUS if you are breastfeeding.

Driving and using machines

There have been cases of dizziness, blurred vision and sleepiness with the use of zoledronic acid as in ZOLEDRONIC ACID FRESENIUS. You should therefore be careful when driving, using machinery or performing other tasks that need full attention.

ZOLEDRONIC ACID FRESENIUS contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially “sodium-free”.

3. How ZOLEDRONIC ACID FRESENIUS is given

You will not be expected to give yourself ZOLEDRONIC ACID FRESENIUS. It will be given to you by a person who is qualified to do so.

ZOLEDRONIC ACID FRESENIUS is administered intravenously (into a vein). Your doctor will decide the appropriate dosage and times of administration.

If you are being treated to reduce the amount of calcium in your blood (for TIH), you will normally only be given one infusion of ZOLEDRONIC ACID FRESENIUS.

Your doctor will also decide how long treatment with ZOLEDRONIC ACID FRESENIUS will last. He/she may decide to alter your dose should you develop any side effects, such as kidney function abnormalities.

ZOLEDRONIC ACID FRESENIUS is usually administered as a 15-minute intravenous infusion, in a separate infusion line, every 3 to 4 weeks. The usual single dose given is 4 mg.

Your doctor will recommend that you drink enough water before each treatment to help prevent dehydration.

If you have the impression that ZOLEDRONIC ACID FRESENIUS is too strong or too weak for you, please discuss this with your treating doctor.

Patients whose blood calcium levels are not too high will also be prescribed calcium and vitamin D supplements to be taken each day.

If you use more ZOLEDRONIC ACID FRESENIUS than you should

Since a healthcare provider will administer ZOLEDRONIC ACID FRESENIUS, he/she will control the dosage. However, in the event of overdosage your doctor will manage the overdosage.

If you forget to use ZOLEDRONIC ACID FRESENIUS

Since a healthcare provider will administer ZOLEDRONIC ACID FRESENIUS, it is unlikely that the dose will be missed.

4. Possible side effects

ZOLEDRONIC ACID FRESENIUS can have side effects.

Not all side effects reported for ZOLEDRONIC ACID FRESENIUS are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking ZOLEDRONIC ACID FRESENIUS, please consult your healthcare provider for advice.

If any of the following happens, tell your doctor immediately:

- swelling of the hands, feet, ankles, face, lips and mouth or throat, which may cause difficulty in swallowing or breathing,
- skin rash with hives, itching.

These are all very serious side effects. If you have them, you may have had a serious reaction to ZOLEDRONIC ACID FRESENIUS. You may need urgent medical attention or further hospitalisation.

Tell your doctor as soon as possible if you notice any of the following:

- Shortness of breath or troubled breathing, coughing, chest pain (scarring and inflammation of the tissue that surrounds the lung's air sacs, blood vessels and airways)
- Blurred vision, painful, red, swollen eyes or eye sockets (conjunctivitis)
- Slow heart rate
- Blood in the urine or inability to pass urine, painful or difficult urination

- Pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth. These could be signs of bone damage in the jaw (osteonecrosis). Tell your doctor and dentist immediately if you experience such symptoms
- Osteonecrosis (bone disease) of the outer ear canal, hip or femur. (See "Special care should be taken with ZOLEDRONIC ACID FRESENIUS")
- Unusual fracture of the thigh bone particularly in patients on long-term treatment for osteoporosis may occur rarely. Contact your doctor if you experience pain, weakness or discomfort in your thigh, hip or groin as this may be an early indication of a possible fracture of the thigh bone.
- Injection site reactions, such as pain, irritation, swelling and induration.
- Swelling of the feet, ankles or lower legs.

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:

<u>Frequent side effects:</u>

- Low level of red blood cells (anaemia)
- Headache
- Conjunctivitis
- Nausea
- Vomiting
- Decreased appetite
- Bone, joint or muscle ache and general pain
- Kidney function affected (you may notice changes in how much you urinate)

- Flu-like syndrome consisting of fever, fatigue, weakness, drowsiness and chills
- Low level of phosphates in blood
- High levels of creatinine and urea in blood.
- Low level of calcium in the blood (hypocalcaemia)

<u>Less frequent side effects</u>

- Blood test deviations: low platelet count (may cause bleeding and excessive bruising), low white cell count (causing you to be more prone to infections)
- Low counts of white blood cells and blood platelets
- Confusion
- Anxiety
- Sleep disturbances (including a strong desire to sleep)
- Dizziness
- Tingling or numbness of the hands or feet
- Taste disturbances
- Abnormal sensitivity to touch
- Tremor
- High blood pressure
- Low blood pressure
- Dry mouth, inflammation of the mouth
- Dyspepsia (indigestion)
- Diarrhoea
- Constipation

- Muscle cramps
- Blood in the urine, kidney failure (some signs may be swelling, tiredness and problems with urination)
- Fanconi syndrome (excess excretion of glucose, bicarbonate, phosphates, uric acid, potassium, and certain amino acids)
- Skin reactions (pain, irritation, hardening of skin, redness and swelling) at the infusion site, rash, itching
- Weight increased
- Low level of magnesium and potassium in the blood. Your doctor will monitor this and take any necessary measures

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects

If you get side effects, talk to your doctor, pharmacist or nurse. You can also report side effects to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of ZOLEDRONIC ACID FRESENIUS

5. How to store ZOLEDRONIC ACID FRESENIUS

Store all medicines out of reach of children.

Store at or below 25 °C. ZOLEDRONIC ACID FRESENIUS does not require any special storage conditions.

After aseptic dilution, it is preferable to use the diluted product immediately. If not used immediately, 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.

If refrigerated, the solution must be allowed to reach room temperature before administration.

Your doctor, pharmacist or nurse knows how to store ZOLEDRONIC ACID FRESENIUS properly (see section 6).

6. Contents of the pack and other information

What ZOLEDRONIC ACID FRESENIUS contains

- The active substance is zoledronic acid. One vial contains 4 mg of zoledronic acid (as monohydrate).
- The other ingredients are mannitol, sodium citrate, water for injections.

What ZOLEDRONIC ACID FRESENIUS looks like and contents of the pack

ZOLEDRONIC ACID 4 mg/5 ml FRESENIUS is a clear colourless solution

ZOLEDRONIC ACID 4 mg/5 ml FRESENIUS is packed in a colourless polypropylene plastic vial with a bromobutyl rubber stopper and an aluminium cap with a plastic flip-off component. It is supplied in packs containing 1, 4 or 10 vials.

Not all pack sizes may be marketed

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Access to the corresponding Professional Information

To be announced.