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1.3 South African Labelling And Packaging

1.3.1 South African Package Insert

1.3.1.1 Package Insert

The package insert follows on page 2.

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PACKAGE INSERT FOR SANDOZ IBANDRONATE 2 mg/2 ml and 6 mg/ 6ml INJECTION

Scheduling status: S4

Proprietary names and dosage forms:

SANDOZ IBANDRONATE 2 mg/2 ml (injection)

SANDOZ IBANDRONATE 6 mg/6 ml (injection)

Composition:

Sandoz Ibandronate 2 mg/2 ml: Each 2 ml ampoule contains 2,25 mg ibandronate sodium monohydrate (equivalent to 2 mg ibandronic acid)**.**

Sandoz Ibandronate 6 mg/6 ml: Each 6 ml vial contains 6,75 mg ibandronate sodium monohydrate (equivalent to 6 mg ibandronic acid).

List of excipients:

Citric acid (monohydrate), sodium chloride, water for injections.

Sugar free.

Pharmacological classification:

A.3.2 Connective tissue medicines. Non-hormonal preparations.

Pharmacological action:

Pharmacodynamic properties:

Ibandronic acid belongs to the group of nitrogen containing bisphosphonates which differ from non-nitrogen containing bisphosphonates with respect to the mechanism of action.

Bisphosphonates have a selective action on bone tissue based on their high affinity for bone mineral. They act by inhibiting osteoclast activity, although the precise mechanism is not clear.

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Pharmacokinetic properties:

Peak levels of ibandronate are reached immediately after completing the injection. The intravenously administered medicine is partially excreted unchanged, mainly via the kidney and the remaining amount is bound to bone tissue. Ibandronic acid is an analogue of pyrophosphonate, but is resistant to chemical and enzyme hydrolysis. Therefore, ibandronic acid is not metabolised once it has entered the systemic circulation. About 10 % binds to blood cells and the blood plasma ratio is approximately 0, 7. The half-life in serum is 31 hours and in urine ranges from 5 to 15 hours. About 40 % of the dose is recovered in urine during the first two hours of infusion. After 24 hours, 61 % of the dose is excreted by the kidneys. Protein binding decreases from 99 % to 50 % in the range from 2 ng/ml to 1000 ng/ml and only the unbound fraction of ibandronic acid is glomerularly filtrated.

Indications:

Treatment of tumour-induced hypercalcaemia, with or without metastases.

Prevention of skeletal complications requiring radiotherapy (or surgery) in patients with breast cancer and bone metastases.

Contra-indications:

SANDOZ IBANDRONATE injection solution must not be used in patients with known hypersensitivity to ibandronate or other bisphosphonates or any of the other excipients.

SANDOZ IBANDRONATE injection solution should not be used during pregnancy and lactation due to lack of clinical experience.

SANDOZ IBANDRONATE injection should not be used in children under 18 years.

Renal function impairment.

Impaired liver function.

Warnings:

Ibandronate injection solution should not be used in children below the age of 18 due to insufficient clinical data on safety and efficacy.

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Renal function, calcium, phosphate and magnesium must be monitored during and after treatment with SANDOZ IBANDRONATE.

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

The inadvertent intra-arterial administration as well as paravenous administration is not recommended. This can lead to tissue damage.

Ensure that SANDOZ IBANDRONATE injection is only administered intravenously.

Interactions:

When SANDOZ IBANDRONATE is administered with aminoglycosides, both agents can lower serum calcium levels for prolonged periods. Attention should also be paid to the possible existence of simultaneous hypomagnesaemia (reduced magnesium levels).

SANDOZ IBANDRONATE injection should not be mixed with calcium containing solutions.

Pregnancy and lactation:

There are no adequate data from use of ibandronic acid in pregnant women. Therefore SANDOZ IBANDRONATE injection solution should not be used during pregnancy.

It is not known whether ibandronic acid is excreted in human milk. SANDOZ IBANDRONATE injection solution should not be used during lactation.

Dosage and directions of use:

Prevention of skeletal events in patients with breast cancer and bone metastases:

Recommended dose is 6 mg given every 3 to 4 weeks administered as intravenous infusion in 100 ml 0,9 % sodium chloride or 100 ml 5 % dextrose solution. The dose should be infused over at least 15 minutes.

Tumour-induced hypercalcaemia: Adults and elderly

Consideration should be given to the severity of hypercalcaemia as well as tumour type. **In general, patients with osteolytic bone metastases require lower doses than patients with the humoral type of hypercalcaemia.**

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Recommended single dose:

Prior to treatment with SANDOZ IBANDRONATE injection solution, the patient should be adequately rehydrated with 0,9 % sodium chloride.

	Albumin-corrected serum calcium* after adequate rehydration	Dose
Severe Hypercalcaemia	≥ 3,5 mmol/l (≥ 12 mg/dl)	2 - 4 mg
Moderate Hypercalcaemia	< 3,5 mmol/l (< 12 mg/dl)	1 - 2 mg

The highest dose used in clinical trials was 6 mg but this dose does not add any further benefit in terms of efficacy.

*** Note**: Albumin-corrected serum calcium (mmol/l) =

serum calcium (mmol/l) - [0,02 x albumin (g/l)] + 0,8

Or

Albumin-corrected serum calcium (mg/dl) =

serum calcium (mg/dl) + 0,8 x [4 - albumin (g/dl)]

To convert the albumin-corrected serum calcium in mmol/l value to mg/dl, multiply by 4.

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

SANDOZ IBANDRONATE injection solution should be administered as an intravenous infusion. The contents of the ampoules/vial are to be added to 500 ml isotonic (0,9 %) sodium chloride or 500 ml 5 % dextrose solution and infused over two hours.

SANDOZ IBANDRONATE injection solution should not be mixed with calcium containing solutions.

After reconstitution: Store at 2 °C - 8 °C (in a refrigerator).

In most cases a raised serum calcium level can be reduced to the normal range within 7 days.

The median time to relapse (return of albumin-corrected serum calcium to levels above 3 mmol/l) was 18 - 19 days for the 2 mg and 4 mg doses. The median time to relapse was 26 days with a dose of 6 mg.

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Repeated treatment may be considered in case of recurrent hypercalcaemia or insufficient efficacy. However, until adequate data has been achieved, do not exceed cumulative dose of 6 mg.

Paediatric use:

Safety and efficacy in individuals less than 18 years old have not been established. Hence treatment in patients less than 18 years old is contra-indicated.

Side effects and special precautions:

Side effects:

Infection and infestation:

Frequent: Infection.

Less frequent: Cystitis, vaginitis, oral candidiasis.

Neoplasms benign and malignant (including cysts and polyps):

Less frequent: Benign skin neoplasm.

Blood and lymphatic system:

Less frequent: Anaemia, blood dyscrasia.

Immune system disorders:

Less frequent: Hypersensitivity, angioedema, anaphylactic reaction/shock.

Endocrine disorders:

Frequent: Parathyroid disorder.

Metabolism and nutrition disorders:

Frequent: Hypocalcaemia.

Less frequent: Hypophosphatemia.

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Psychiatric disorders:

Less frequent: Sleep disorder, anxiety, affection lability.

Nervous system disorders:

Frequent: Headache, dizziness, dysgeusia (taste perversion).

Less frequent: Cerebrovascular disorder, nerve root lesion, amnesia, migraine, neuralgia, hypertonia, hyperaestesia, paraesthesia circumoral, parosmia.

Eye disorders:

Frequent: Cataract.

Less frequent: Ocular inflammation.

Ear and labyrinth disorders:

Less frequent: Deafness.

Cardiac disorders:

Frequent: Bundle branch block.

Less frequent: Myocardial ischaemia, cardiovascular disorder, palpitations.

Vascular disorders:

Less frequent: Hypertension, lymphoedema, varicose veins.

Respiratory, thoracic and mediastinal disorders:

Frequent: Pharyngitis.

Less frequent: Lung oedema, stridor, bronchospasm.

Gastrointestinal disorders:

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Frequent: Diarrhoea, vomiting, dyspepsia, gastrointestinal pain, tooth disorder.

Less frequent: Gastroenteritis, dysphagia, gastritis, mouth ulceration, cheilitis.

Hepato-biliary disorders:

Less Frequent: Cholelithiasis.

Skin and subcutaneous tissue disorders:

Frequent: Skin disorder, ecchymosis.

Less frequent: Rash, alopecia.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Myalgia, arthralgia, joint disorder, osteoarthritis, bone pain.

Less frequent: Atypical subtrochanteric and diaphyseal femoral fractures, osteonecrosis of jaw.

Renal and urinary disorders:

Less frequent: Urinary retention, renal cyst.

Reproductive system and breast disorders:

Less frequent: Pelvic pain.

General disorders and administration site conditions:

Frequent: Asthaenia, influenza-like illness, pyrexia, peripheral oedema, thirst.

Less frequent: Hypothermia, rigors.

Investigations:

Frequent: Increased gamma-GT, increased creatinine.

Less frequent: Blood alkaline phosphatase increase, weight decrease.

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Injury, poisoning and procedural complications:

Less frequent: Injury, injection site pain.

Special precautions:

Hypocalcaemia and other disturbances of bone and mineral metabolism should be effectively treated before starting SANDOZ IBANDRONATE therapy for metastatic bone disease.

Frequently, decreased renal calcium excretion is accompanied by a fall in serum phosphate levels not requiring therapeutic measures. The serum calcium level may fall to hypocalcaemic values.

Adequate intake of calcium and vitamin D is important in all patients. Patients should receive supplemental calcium and/or vitamin D if dietary intake is inadequate.

Osteonecrosis of the jaw generally associated with tooth extraction and/or local infection (including osteomyelitis) may occur in patients also receiving chemotherapy and corticosteroids.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with SANDOZ IBANDRONATE in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene).
Invasive dental procedures should be avoided in patients with concomitant factors if possible while on SANDOZ IBANDRONATE treatment.
For patients who develop osteonecrosis of the jaw while on SANDOZ IBANDRONATE therapy, dental surgery may exacerbate the condition. Clinical judgement of the treating medical practitioner should guide the management plan of each patient based on individual benefit/risk assessment.

Administration of SANDOZ IBANDRONATE may result in broncho-constriction in acetylsalicylic acid-sensitive asthmatic patients.

Effects on ability to drive and use machines:

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SANDOZ IBANDRONATE may influence the ability to drive and use machines. SANDOZ IBANDRONATE can cause headache and dizziness.

Known symptoms of overdosage and particulars of its treatment:

Overdose:

Up to now there is no experience of acute poisoning with SANDOZ IBANDRONATE injection solution. Since both the kidney and the liver were found to be target organs for toxicity, kidney and liver function should be monitored. Clinically relevant hypocalcaemia should be corrected by intravenous administration of calcium gluconate.

Treatment should be symptomatic and supportive.

Identification:

Sandoz Ibandronate 2 mg/2 ml: A sterile, clear, colourless solution, free from visible particles.

Sandoz Ibandronate 6 mg/6 ml: A sterile, clear, colourless solution, free from visible particles.

Presentation:

Sandoz Ibandronate 2 mg/2 ml is packed in a 3 ml colourless OPC (one-point-cut) type 1, glass ampoule coded with one blue ring at the tip.

Sandoz Ibandronate 6 mg/6 ml is packed in a 10 ml colourless type 1, glass vial closed with bromobutyl rubber stoppers and sealed with aluminium caps provided with polyethylene flip cap.

Storage instructions:

Store at or below 25 ˚C.

After reconstitution: Store at 2 °C - 8 °C (in a refrigerator) and use within 24 hours.

Keep out of the reach and sight of children.

The unused content must be discarded after initial opening of the ampoule/ vial.

Registration numbers:

Sandoz Ibandronate 2 mg/2 ml: 44/3.2/0258

Sandoz Ibandronate 6 mg/6 ml: 44/3.2/0259

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Name and business address of the holder of the certificates of registration:

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Date of publication of this package insert:

5 December 2013