PROFESSIONAL INFORMATION FOR ZORIKOS 100 and 300

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ZORIKOS 100 tablets
ZORIKOS 300 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of ZORIKOS 100 contains 100 mg of allopurinol.
Each tablet of ZORIKOS 300 contains 300 mg of allopurinol.

ZORIKOS 100 contains sugar (lactose monohydrate, 37,26 mg per tablet).
ZORIKOS 300 contains sugar (lactose monohydrate, 111,80 mg per tablet).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

ZORIKOS 100: White to off white, scored, flat cylindrical tablet debossed with “I” and “56” on either side of the break line on one side, and plain on other side.

ZORIKOS 300: White to off white, scored, flat cylindrical tablet debossed with “I” and “57” on either side of the break line on one side, and plain on other side.

4. CLINICAL PARTICULARS

4.1Therapeutic indications

ZORIKOS is indicated for the treatment of gout and hyperuricaemia associated with other conditions. It reduces the concentration of uric acid in plasma with gradual resolution of tophi and reduces the risk of the formation of uric acid calculi. It may be effective in patients with impaired renal function.

Treatment of hyperuricaemia associated with leukaemia or resulting from radiotherapy or the use of anti-neoplastic agents such as mercaptopurine or during treatment with diuretics of the thiazide or similar type.

4.2 Posology and method of administration

Posology:

It is important to ensure sufficient fluid intake to maintain a daily urinary volume above 2 litres, especially in children with Lesch-Nyhan syndrome.

Adults:

Gout:

It is usual to commence with 50 mg twice daily and to increase this dose as required up to 200 mg to 400 mg daily in divided doses. In severe conditions, doses of up to 600 mg may be necessary.

Hyperuricaemia associated with leukaemia:

The recommended starting dose for ZORIKOS is 200 mg three times a day, starting at least 2 – 3 days before chemotherapy or starting treatment with anti-neoplastic medicines. The dose should be adjusted until a maintenance dose of 300 – 400 mg daily.

If a dosage is required per bodyweight, 2 – 10 mg/kg bodyweight per day is used, up to a maximum dose of 900 mg per day.

Special populations

Elderly:

Due to limited data, it is recommended to prescribe the lowest dosage of ZORIKOS required to produce adequate urate reduction.

Renal Impairment:

Allopurinol, as in ZORIKOS, and oxipurinol are excreted via the kidneys. Patients with impaired renal function require a reduction in the dosage, based on the creatinine clearance.

Creatinine clearance dosage:

- 10–20 mL/minute: 200 mg daily.
- Less than 10 mL/minute: A maximum dose of 100 mg daily.
- Less than 3 mL/minute: A longer dosage interval is required.

Allopurinol and oxipurinol are effectively removed from plasma by renal dialysis. For patients receiving dialysis 2 – 3 times a week, an alternative dosing regimen is required of 300 – 400 mg of ZORIKOS immediately after each dialysis. Do not administer ZORIKOS during dialysis.

Dosage in hepatic impairment:

The dosage of ZORIKOS should be reduced in patients with hepatic impairment.
During the initial stages of treatment, periodic liver function tests are recommended.

Paediatric population

Children under 15 years: 10–20 mg/kg per day, up to a maximum dose of 400 mg daily. The use of ZORIKOS in children is indicated in malignant conditions (for example, leukaemia) and certain enzyme disorders (for example, Lesch-Nyhan syndrome).

Method of administration:

For oral administration.

4.3 Contraindications

- Hypersensitivity to allopurinol or any of the inactive excipients of ZORIKOS in section 6.1.
- Lactating women (see section 4.6).
- Children, except those with a malignancy.

4.4 Special warnings and precautions for use

Hypersensitivity syndrome, Stevens-Johnson Syndrome and Toxic epidermal necrolysis:

ZORIKOS hypersensitivity can manifest in many different ways, including maculopapular exanthema, a delayed multi-organ hypersensitivity syndrome (also known as DRESS) and life-threatening skin reactions including Stevens- Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

The signs and symptoms of SJS and TEN include a progressive skin rash with blisters or mucosal lesions including arthralgia, eosinophilia, exfoliation, fever and/or lymphadenopathy. Drug rash with eosinophilia and systematic syndrome (DRESS) is characterised by various combinations of signs and symptoms including arthralgia, eosinophilia, fever, hepato-splenomegaly, leucopenia, abnormal liver function tests, lymphadenopathy, pseudo lymphoma, rashes, vanishing bile duct syndrome and vasculitis (see section 4.8).

On the clinical diagnosis and presentations of these reactions, at any time during therapy, ZORIKOS should be discontinued immediately and permanently. Do not restart ZORIKOS in patients who have been diagnosed with hypersensitivity syndrome and SJS/TEN. These hypersensitivity reactions may be overcome with the initiation of corticosteroid therapy (see section 4.8).

HLA-B*5801 allele:
Patients with the HLA-B*5801 allele have an increased risk of developing allopurinol associated hypersensitivity syndrome and SJS/TEN. The incidence of the HLA- B*5801 allele differs amongst ethnic populations:

- **Ethnic population percentage:**

Han Chinese: 20 %; Korean: 12 %; Japanese or European origin: 1–2 %

Genotyping may be used as a screening tool to make decisions on initiating therapy with ZORIKOS. The benefits should outweigh the risks, if ZORIKOS is required to be used in patients who are known carriers of the HLA-B*5801 allele. These patients should be closely monitored for the signs of hypersensitivity syndrome or SJS/TEN and advised to stop treatment immediately and permanently at the first appearance of symptoms.

Chronic renal impairment:
ZORIKOS associated hypersensitivity reactions, including SJS/TEN, occur at a higher risk in patients with chronic renal impairment. These patients should be closely monitored for the signs of hypersensitivity syndrome or SJS/TEN and advised to stop treatment immediately and permanently at the first appearance of symptoms.

Hepatic or renal impairment:
Patients with hepatic or renal impairment require a reduction in the dose of ZORIKOS. Extra care is required when prescribing ZORIKOS in patients under treatment for hypertension or cardiac insufficiency, for example with diuretics or ACE inhibitors, as both these medicines cause renal impairment.

Asymptomatic hyperuricaemia:
ZORIKOS should not be used in asymptomatic hyperuricaemia. To correct this condition, it is required to adjust the diet and increase fluid intake, together with management of the underlying cause.

Acute gout attacks:
ZORIKOS should not be initiated until an acute attack has completely subsided in patients with chronic gout, as allopurinol may precipitate further acute attacks. Treatment of an acute attack should be initiated with a low dose of NSAIDs (not aspirin or salicylates) or colchicine for at least one month after hyperuricaemia has been improved. If an acute attack occurs in patients on ZORIKOS therapy, continue treatment at the same dosage while the acute attack is treated with a suitable anti-inflammatory medicine.

Xanthine deposition:
The concentration of xanthine in urine may increase sufficiently in conditions which
greatly increase the rate of urate formation (for example, malignant disease and its treatment, Lesch-Nyhan syndrome), resulting in its deposition in the urinary tract. Adequate fluid intake is recommended to maintain urine dilution to decrease the risk.

Impaction of uric acid renal stones:
Impaction of the ureter may occur when large uric acid renal pelvic stones are dissolved by ZORIKOS therapy.

Thyroid disorders:
Increased TSH values (>5,5 µIU/mL) were observed in patients on long-term treatment with allopurinol, as in ZORIKOS. Caution is required when ZORIKOS is used in patients with alteration of thyroid function.

Important information about some of the ingredients of ZORIKOS
ZORIKOS contains lactose and should not be prescribed in patients with rare hereditary conditions including galactose intolerance, e.g. galactosaemia, glucose- galactose malabsorption or the Lapp lactase deficiency.

4.5 Interaction with other medicines and other forms of interaction
6-mercaptopurine and azathioprine:
6-mercaptopurine and azathioprine are inactivated by xanthine oxidase. When used in combination with ZORIKOS, the activity of these substances is prolonged. The usual dose of 6-mercaptopurine and azathioprine should be decreased.

Ampicillin / amoxicillin:
There is an increase in the occurrence of a skin rash in patients using ampicillin or amoxicillin together with ZORIKOS. It is recommended that an alternative to ampicillin or amoxicillin be prescribed.

Chlorpropamide:
Chlorpropamide and ZORIKOS may compete for excretion in the renal tubule. When this combination is used in patients with impaired renal function, the hypoglycaemic effect of chlorpropamide may be extended.

Ciclosporin:
Ciclosporin plasma levels may be increased when used in combination with ZORIKOS, possibly resulting in ciclosporin toxicity.

Coumarin anticoagulants:
There may be an increase in the effects of warfarin and other coumarin anticoagulants when used with ZORIKOS. Close monitoring of the anticoagulant activity is required in patients receiving this combination.

Cytostatics:
With administration of ZORIKOS and cytostatics (for example, bleomycin, cyclophosphamide, doxorubicin, mechlorethamine, procarbazine, alkyl halogenides), blood dyscrasias occur more frequently than when these medicines are administered alone. Blood count monitoring should therefore be performed at regular intervals. ZORIKOS does not appear to increase the toxic effects of these medicines.

Didanosine:
Didanosine plasma concentrations are increased when used in combination with ZORIKOS. This combination is not recommended, but if unavoidable, the dose of didanosine should be reduced. Patients receiving this combination should be closely monitored.

Diuretics:
An interaction between allopurinol, as in ZORIKOS, and furosemide that results in increased serum urate and plasma oxypurinol concentrations has been reported. An increased risk of hypersensitivity has been reported when ZORIKOS is given with diuretics, in particular thiazides, especially in renal impairment.

ACE inhibitors:
An increased risk of hypersensitivity has been reported when ZORIKOS is given with ACE inhibitors, especially in renal impairment.

Aluminium hydroxide:
If aluminium hydroxide is taken concomitantly, ZORIKOS may have an attenuated effect. There should be an interval of at least 3 hours between taking both medicines.

Phenytoin:
The hepatic oxidation of phenytoin may be inhibited by ZORIKOS, but this interaction has not been shown to be clinically significant.

Salicylates and uricosuric medicines:
Large doses of salicylates and uricosuric medicines (for example, probenecid) may increase the renal excretion of oxipurinol, the active metabolite of allopurinol. This effect may reduce the therapeutic effect of ZORIKOS.

Theophylline:
The metabolism of theophylline may be inhibited when used in combination with ZORIKOS. The plasma levels of theophylline must be closely monitored in patients being started on, or receiving an increased dose in ZORIKOS therapy.

Vidarabine:
The plasma half-life of vidarabine (adenine arabinoside) may be increased when used in combination with ZORIKOS. Close monitoring is advised when this combination is prescribed to prevent toxic effects.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no adequate data on the use of ZORIKOS in pregnant women. ZORIKOS should only be used in pregnant women when there is no safer alternative therapy available, or when the disease carries a risk to the mother and unborn child.

Breastfeeding
Allopurinol and oxipurinol pass into the breast milk. Therefore, ZORIKOS should not be used during breastfeeding (see section 4.3).

4.7 Effects on ability to drive and use machines:
ZORIKOS may cause ataxia, somnolence and vertigo. Therefore, patients should be advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether ZORIKOS affects their ability to perform such activities.

4.8 Undesirable effects
The side effects associated with ZORIKOS are rare, and are typically negligible. Patients with renal and/or hepatic impairment are at a higher risk of experiencing adverse effects.

System Organ Class	Frequency	Adverse drug reaction
Infections and infestations	Less frequent	Furunculosis
Blood and lymphatic system disorders	Less frequent	Agranulocytosis, aplastic anaemia, thrombocytopenia (these side effects have been particularly reported in patients with impaired renal and/or hepatic function)
Immune system disorders	Less frequent	Angioimmunoblastic lymphadenopathy*,

		hypersensitivity reactions** angioedema.
Metabolism and nutrition disorders	Less frequent	Diabetes mellitus, hyperlipidaemia
Psychiatric disorders	Less frequent	Depression
Nervous system disorders	Less frequent	Ataxia, coma, headache, neuropathy, paralysis, paraesthesia, somnolence and taste perversion
Eye disorders	Less frequent	Cataract, macular changes, visual disorder
Ear and labyrinth disorders	Less frequent	Vertigo
Cardiac disorders	Less frequent	Angina pectoris, bradycardia
Vascular disorders	Less frequent	Hypertension
Gastrointestinal disorders	Less frequent	Abdominal pain, changed bowel habit, diarrhoea, gastric irritation, nausea, recurrent haematemesis, steatorrhoea, stomatitis, vomiting
Hepato-biliary disorders	Less frequent	Asymptomatic increases in liver function tests, hepatitis (including hepatic necrosis and granulomatous hepatitis
Skin and subcutaneous tissue disorders	Frequent Less frequent	Rash Alopecia, discoloured hair, fixed drug eruption, Stevens-Johnson syndrome/toxic epidermal necrolysis
Renal and urinary disorders	Less frequent	Haematuria, uraemia
Reproductive system and breast disorders	Less frequent	Erectile dysfunction, gynaecomastia, male infertility
General disorders and administration site conditions	Less frequent	Asthenia, fever, general malaise, oedema

* Angioimmunoblastic lymphadenopathy may occur following biopsy of a generalised lymphadenopathy. This effect will be reversed when ZORIKOS is discontinued.

**Hypersensitivity reactions of the skin and blood include skin eruptions, fever, chills, leukopenia or leucocytosis and eosinophilia, arthralgia and vasculitis leading to renal and hepatic damage. These reactions may be severe, and even fatal (see section 4.4).

Description of selected adverse drug reactions

Immune system disorders:

Angioimmunoblastic lymphadenopathy may occur following biopsy of a generalised lymphadenopathy. This effect will be reversed when ZORIKOS is discontinued.

Hypersensitivity reactions of the skin and blood include skin eruptions, fever, chills, leukopenia or leucocytosis and eosinophilia, arthralgia and vasculitis leading to renal and hepatic damage. These reactions may be severe, and even fatal (see section 4.4)

Skin and subcutaneous tissue disorders:

The rash is commonly pruritic, maculopapular, sometimes scaly, sometimes purpuric and rarely exfoliative, such as Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN). Upon diagnosis of SJS/TEN occurring at any time during treatment, ZORIKOS should be immediately and permanently discontinued (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine.Health care professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms:

The most common adverse events associated with an overdosage ZORIKOS are diarrhoea, dizziness, nausea and vomiting.

Symptoms and signs of overdose including nausea, vomiting, diarrhoea and dizziness have been reported. Recovery followed general supportive measures. Massive absorption of ZORIKOS may lead to considerable inhibition of xanthine oxidase activity, which should have no untoward effects unless affecting concomitant medication, especially with 6-mercaptopurine and/or azathioprine.
Adequate hydration to maintain optimum diuresis facilitates excretion of allopurinol and its metabolites. If considered necessary haemodialysis may be used.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

A3.3 Antigout preparations.

Mechanism of action

Allopurinol is a xanthine-oxidase inhibitor.

Allopurinol and its main metabolite, oxipurinol, act by inhibiting the enzyme xanthine oxidase, responsible for catalysing the oxidation of hypoxanthine to xanthine, and xanthine to uric acid. This results in decreased levels of uric acid in the blood and urine. In some hyperuricaemic patients, in addition to purine catabolism, the purine biosynthesis may also be reduced due to feedback inhibition of hypoxanthine-guanine phosphoribosyl transferase.

5.2. Pharmacokinetic properties

Absorption:

Following oral administration, allopurinol is rapidly absorbed from the gastrointestinal tract, with detectable levels occurring within 30–60 minutes. The oral bioavailability of allopurinol ranges from 67–90 %. The peak plasma concentration is reached within 1,5 hours. However, this level is known to decrease rapidly, exhibiting barely measurable levels after 6 hours. Oxipurinol exhibits a more sustained concentration, reaching peak plasma levels within 3–5 hours following oral administration.

Distribution:

Allopurinol is not significantly bound to plasma proteins. In humans, extensive reuptake by tissues is suggested, with an apparent volume of distribution of approximately 1,6 litres/kilogram. The highest concentration of allopurinol and oxipurinol is likely to be in the liver and intestinal mucosa, where the activity of xanthine oxidase is high.

Biotransformation and elimination:

Approximately 20 % of the administered dose is excreted in the faeces. The elimination of the absorbed dose is primarily via conversion to its main metabolite, oxipurinol, by xanthine oxidase and aldehyde oxidase, with less than 10 % eliminated via renal excretion as unchanged allopurinol. Other metabolites of allopurinol include allopurinol-riboside and oxipurinol-7-riboside. Allopurinol has plasma half-life of 0,5 to 1,5 hours.

The metabolite, oxipurinol, is a less potent inhibitor of xanthine oxidase, with a prolonged plasma half-life of 13–30 hours. Inhibition of the enzyme, xanthine oxidase, is therefore maintained over 24 hours following a single dose. Patients with normal renal function will gradually accumulate oxipurinol, until a steady-state plasma concentration is reached. In these patients, when a dose of 300 mg once daily is administered, plasma concentrations are generally 5–10 mg/litre.

Oxipurinol is eliminated unchanged, in the urine. It undergoes tubular reabsorption, which extends the half-life. The elimination half-life ranges from 13,6–29 hours. The wide range in the half-life may be due to the variation in study design and/or in the creatinine clearance in patients.

Special populations

Renal Impairment:

Patients with impaired renal function have a significantly reduced clearance of allopurinol and oxipurinol, resulting in increased plasma levels with chronic therapy. In patients with a creatinine clearance of 10–20 mL/min, oxipurinol concentrations of 30 mg/litre have been established with chronic therapy of a dose of 300 mg of allopurinol once daily. These levels are equivalent to a dose of 600 mg/day in patients with normal renal function. A reduction in the dose is required (see section 4.2).

Elderly:

There are no relevant age-dependent differences observed in the pharmacokinetics of ZORIKOS, unless renal function is compromised.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate
Magnesium stearate
Maize starch
Povidone (K-30)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

48 months

6.4. Special precautions for storage
Store at or below 30 ºC
Protect from light and moisture.
Keep the blister strips in the outer carton until required for use.

6.5. Nature and contents of container
Aluminium and clear, PVC blister strip containing 10 tablets per blister strip. Blister strips are packed into a cardboard carton.

Pack sizes: 30, 60 and 100 tablets.
Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling
Not applicable

7. HOLDER OF THE CERTIFICATE OF REGISTRATION
Forrester Pharma (Pty) Ltd
2 Waterford Mews
Waterford Place
Century City
7441
Cape Town
South Africa

8. REGISTRATION NUMBERS
ZORIKOS 100: 49/3.3/0913
ZORIKOS 300: 49/3.3/0914

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of registration: 12 November 2019
Publication date: January 2022

ZORIKOS 100: Namibia Reg. No.: 21/3.3/0080	NS2
ZORIKOS 300: Namibia Reg. No.: 21/3.3/0081	NS2