Approved Professional Information for Medicines for Human Use:

MIRPOLYZ 100 mg and 300 mg

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

MIRPOLYZ 100 mg tablets

MIRPOLYZ 300 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each MIRPOLYZ 100 mg tablet contains: 100 mg allopurinol.

Each MIRPOLYZ 300 mg tablet contains: 300 mg allopurinol.

Contains sugar (lactose monohydrate):

Each MIRPOLYZ 100 mg tablet contains: 52,03 mg lactose monohydrate.

Each MIRPOLYZ 300 mg tablet contains: 153,60 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

MIRPOLYZ 100 mg tablets

White to off-white coloured, round, biconvex uncoated tablets with ‘AL’ and ‘100’ separated by a breakline on one side and plain on the other side.

MIRPOLYZ 300 mg tablets

Peach coloured, round, biconvex uncoated tablets with ‘AL’ and 300 separated by a breakline on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MIRPOLYZ is used to reduce urate concentrations in body fluids and/or urine to prevent or reverse the deposition of urate/uric acid.

MIRPOLYZ is indicated in:

- the management of the main clinical manifestations of urate deposition which are: gouty arthritis, skin tophi, idiopathic gout, uric acid lithiasis and acute uric acid nephropathy.
- the management of patients with neoplastic and myeloproliferative disease with high cell turnover rates which cause elevations of serum and urinary levels. These include leukaemia, lymphomas, or other malignancies, especially when cytotoxic therapy has been initiated.
- the management of patients with recurrent mixed calcium oxalate renal stones in the presence of hyperuricosuria when fluid, dietary and similar measures have failed.

4.2 Posology and method of administration

Posology

The dose should be titrated against the patient by monitoring serum urate/uric acid and/or urinary uric acid levels at appropriate intervals. Up to and including 300 mg MIRPOLYZ may be taken once a day. Larger doses should be administered as divided doses of not more than 300 mg. It is recommended that MIRPOLYZ be taken after meals for better tolerance.

Adults:

Daily oral dose 100 to 900 mg depending on severity of the condition or 2 to 10 mg/kg bodymass/day.

Special populations

Renal impairment

Dose precautions in renal disorder: Since allopurinol and its metabolites are excreted by the kidney, renal failure may lead to the retention of the medicine and its metabolites with consequent prolongation of plasma half-lives. To reduce attendant risks, the amount and frequency of the dosage may require reduction. The following schedule is provided for guidance in adults: If creatinine clearance exceeds 20 mL/minute - give standard dose. If creatinine clearance is between 10 and 20 mL/minute - give 100 to 200 mg/day. If creatinine clearance is less than 10 mL/minute - give 100 mg/day or at longer intervals. If plasma monitoring facilities are available, plasma oxypurinol levels should be maintained below 100 micromol/litre (15,2 micrograms/mL).

Dose precautions in renal dialysis: Allopurinol and its metabolites are removed by renal dialysis and dosages should be adjusted accordingly. Consideration should be given to an alternative dosage schedule of 300 to 400 mg MIRPOLYZ immediately after each dialysis.

Paediatric population

Children under 15 years:

Daily oral dose 100 to 400 mg or 10 to 20 mg/kg bodymass/day.

Method of administration

MIRPOLYZ is for oral administration

4.3 Contraindications

- Hypersensitivity to allopurinol and any of the excipients listed in section 6.1.
- Severe hepatic or renal disorder.
- An acute gout attack.
- Lactating mothers (see section 4.6)
- Children, except those with malignancy

4.4 Special warnings and precautions for use

- Serious allergic reactions may occur including exfoliative rashes, Stevens-Johnson syndrome and toxic epidermal necrolysis. Should a skin rash or other evidence of sensitivity occur, MIRPOLYZ should be withdrawn immediately (see section 4.8).
- Other hypersensitivity responses may occur e.g. skin eruptions, fever, chills, leukopenia or leucocytosis and eosinophilia, arthralgia and vasculitis leading to renal and hepatic damage. These reactions may be severe, even fatal and may occur at any time during treatment. Patients with renal impairment or taking thiazide diuretics are at special risk. These reactions usually subside a few days after administration is stopped (see section 4.8).
- Treatment with MIRPOLYZ should not be started until an acute attack of gout has completely subsided as this can exacerbate the attack. When starting treatment with MIRPOLYZ, mobilisation of urate deposition may result in exacerbation of attacks of acute gouty arthritis. It is hence advisable to give colchicine at prophylactic doses or an anti-inflammatory medicine for at least one month when starting therapy with MIRPOLYZ. This effect can also be minimised by using small initial doses (100 mg per day) of MIRPOLYZ and gradual increasing of the dose at intervals. If an acute attack of gout develops while the patient is receiving MIRPOLYZ, therapy should be continued at the same dosage and the acute attack treated separately.
- When MIRPOLYZ is used concurrently with azathioprine or mercaptopurine, the dosage of azathioprine or mercaptopurine must be reduced to one-fourth of the usual dose due to prolongation of activity of these medicines (see section 4.5).
- Treatment of neoplasia: Prior to instituting cytotoxic therapy, it is advisable to assess existing serum urate and urinary acid levels. Hyperuricaemia and/or hyperuricosuria should be corrected prior to starting treatment. Adequate hydration to maintain maximum diuresis throughout is important.

- Renal impairment: In patients with impaired renal function, reduced doses should be used (see section 5.1, Pharmacokinetics in patients with renal impairment; see section 4.2).
- Hepatic impairment: MIRPOLYZ should be used with caution.
  Reduced doses should be used.
- Fluid intake should be sufficient to maintain daily urinary volume above 2 litres. Taking allopurinol after food minimises gastric irritation.
- A possibility of xanthine stone formation exists in children with Lesch-Nyhan syndrome. This can be minimised by alkalinisation of the urine and increasing daily fluid intake.
- Adequate therapy with MIRPOLYZ will lead to dissolution of large uric acid renal pelvic stones, with the remote possibility of impaction in the ureter.
- Increased TSH (thyroid stimulating hormone) values (> 5,5 µIU/mL) were observed in patients on long-term treatment with allopurinol. Caution is required when MIRPOLYZ is used in patients with alteration of thyroid function

MIRPOLYZ contains lactose; thus, patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take MIRPOLYZ.

4.5 Interaction with other medicines and other forms of interaction

- If aluminium hydroxide is taken concomitantly, allopurinol may have an attenuated effect. There should be an interval of at least 3 hours between taking both medicines.
- Azathioprine is metabolised to 6-mercaptopurine by xanthine oxidase. Inhibition of this enzyme by MIRPOLYZ results in prolongation of the activity of azathioprine and mercaptopurine and hence the dosage of azathioprine or mercaptopurine must be reduced to one-fourth of the usual dosage when these medicines are given concomitantly with MIRPOLYZ (see section 4.4).
- Concurrent usage of cyclophosphamide and other anti-neoplastic medicines such as doxorubicin, bleomycin, procarbazine and mechlorethamine with MIRPOLYZ, may cause an increase in the toxicity of these anti-neoplastic medicines. Allopurinol may reduce the

clearance of theophylline and other xanthines and their dosage might have to be reduced to avoid toxicity.

- Administration of MIRPOLYZ concomitantly with chlorpropamide may lead to prolonged hypoglycaemic action since there may be competition in the renal tubule for the excretion of chlorpropamide. Poor renal function may exacerbate this further.
- Oxypurinol, the major active metabolite of allopurinol, is excreted by the kidney in a very similar way to urate. Medicines with uricosuric activity such as probenecid or large doses of salicylates may accelerate the excretion of oxypurinol. This may lead to partial loss of therapeutic activity of MIRPOLYZ, but the significance of this needs to be assessed in each case.
- An increase in hypersensitivity reactions, and possibly other side effects, may occur in patients taking MIRPOLYZ with an ACE inhibitor or a thiazide diuretic. Care is advised during concomitant use of an ACE inhibitor or a thiazide diuretic with MIRPOLYZ, particularly in patients with renal impairment.
- There is no evidence that an interaction between allopurinol and the coumarins (such as warfarin) seen under experimental conditions, has any clinical significance. However, all patients receiving anticoagulants concomitantly with MIRPOLYZ should be carefully monitored.
- There may be an increased incidence of skin rashes in patients receiving amoxicillin or ampicillin concomitantly with MIRPOLYZ. In patients receiving therapy with MIRPOLYZ, it is recommended that an alternative to amoxicillin or ampicillin is utilised.
- As evidence suggests that the plasma half-life of vidarabine (adenine arabinoside) is increased in the presence allopurinol, additional vigilance for increased toxic effects is recommended during concomitant use of MIRPOLYZ and vidarabine.
- Concomitant use of didanosine and MIRPOLYZ is not recommended due to possible increases in C_{max} and AUC values of didanosine during concomitant therapy. If co-

administration cannot be avoided, a dose reduction of didanosine may be required and close monitoring of the patient is advised.

- MIRPOLYZ may inhibit the hepatic oxidation of phenytoin, but the clinical significance has not been determined.
- Plasma concentrations of ciclosporin may be increased during concomitant treatment with allopurinol. The possibility of enhanced ciclosporin toxicity should be considered during co-administration of ciclosporin and MIRPOLYZ.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of MIRPOLYZ in human pregnancy has not been established.

Breastfeeding

Allopurinol and oxypurinol have been detected in human breast milk. Use of MIRPOLYZ in lactating mothers is contraindicated (see section 4.3).

4.7 Effects on ability to drive and use machines

Adverse effects such as headaches, drowsiness and vertigo have been reported in patients receiving allopurinol. Patients should exercise caution before driving and using machinery until they are certain that MIRPOLYZ does not adversely affect performance.

4.8 Undesirable effects

b) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and post market spontaneous reports with Allopurinol.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**

Infections and infestations		Furuncle	
Blood and lymphatic system disorders		Agranulocytosis Aplastic anaemia Thrombocytopenia Leukopenia, leucocytosis, eosinophilia	
Immune system disorders		Hypersensitivity Angioimmunoblastic T-cell lymphoma Anaphylactic reaction	
Metabolism and nutrition disorders		Diabetes mellitus, hyperlipidaemia, taste perversion	
Psychiatric disorders		Depression	
Nervous system disorders		Coma Paralysis Ataxia Neuropathy peripheral Paraesthesia Somnolence Headache Dysgeusia Peripheral neuritis, drowsiness, epilepsy	Aseptic meningitis
Eye disorders		Cataract Visual impairment	

		Maculopathy	
Ear and labyrinth disorders		Vertigo	
Cardiac disorders		Angina pectoris Bradycardia	
Vascular disorders		Hypertension	
Gastrointestinal disorders		Vomiting, Nausea, Diarrhoea Haematemesis Steatorrhoea Stomatitis Change of bowel habit	Abdominal pain, gastric irritation, diarrhoea
Hepatobiliary disorders		Liver function test abnormal Hepatitis (including hepatic necrosis and granulomatous hepatitis)	
Skin and subcutaneous tissue disorders	Rash	Stevens-Johnson syndrome/toxic epidermal necrolysis Angioedema Drug eruption Alopecia Hair colour changes Exfoliative rashes	
Musculoskeletal and connective tissue disorders		Arthralgia	

Renal and urinary disorders		Haematuria, Azotaemia, Uraemia	
Reproductive system and breast disorders		Infertility male Erectile dysfunction Gynaecomastia Impotence	
General disorders and administration site conditions		Oedema Malaise Asthenia Pyrexia	
Investigations	Blood thyroid stimulating hormone increased		

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. Healthcare professionals are asked to report any suspected adverse reactions 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

4.9 Overdose

Symptoms

The most likely reaction to allopurinol overdose would be gastro-intestinal intolerance. Nausea, vomiting, diarrhoea and dizziness have been reported in a patient who ingested 20 g of allopurinol.

Management

Administer sufficient fluids to maintain maximum diuresis since this in turn facilitates excretion of allopurinol and its metabolites.

Treatment is symptomatic and supportive.

If considered necessary, haemodialysis may be used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 3.3 Antigout preparations

Pharmacotherapeutic group: Preparations inhibiting uric acid production

ATC code: M04AA01.

Allopurinol is a xanthine oxidase inhibitor. Allopurinol is also a substrate for xanthine oxidase and the product of this reaction is the metabolite oxypurinol, which is also an inhibitor of xanthine oxidase.

Allopurinol and its main metabolite, oxypurinol inhibit the enzyme xanthine oxidase, preventing the oxidation of hypoxanthine to xanthine and xanthine to uric acid. As a result of inhibition of this enzyme responsible for the terminal steps in uric acid biosynthesis, plasma and urine uric acid concentrations are reduced.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, allopurinol is well absorbed with peak plasma concentrations reached within 60 to 90 minutes. Oral bioavailability is up to 90 %.

Distribution

Allopurinol and its active metabolite, oxypurinol are distributed in total tissue water, with the

exception of the brain, where their tissue concentrations are one-third of those in other tissues. The apparent volume of distribution is approximately 1,6 litre/kg.

Neither compound is bound to plasma proteins.

It is likely that allopurinol and oxypurinol will be present in the highest concentrations in the liver and intestinal mucosa as these are areas where xanthine oxidase activity is high.

Biotransformation

Allopurinol has a plasma half-life of about 1 to 2 hours and most of its pharmacological activity is due to its metabolite, oxypurinol which has estimated plasma half-life of 18–30 hours (prolonged further in renal impairment). This provides effective inhibition of xanthine oxidase maintained over a 24-hour period with a single daily dose of MIRPOLYZ. In patients with normal renal function, oxypurinol will accumulate until a steady-state plasma oxypurinol concentration is reached. Such patients, taking 300 mg of allopurinol per day, will generally have plasma oxypurinol concentrations of 5-10 mg/litre. Both allopurinol and oxypurinol are conjugated to form their respective ribonucleosides.

Elimination

Faecal elimination accounts for approximately 20 % of the ingested dose of allopurinol and 10–30 % is excreted unchanged in the urine. The remainder undergoes metabolism. Oxypurinol is eliminated unchanged in the urine but has a long elimination half-life as it is slowly excreted via glomerular filtration and undergoes tubular reabsorption.

Pharmacokinetics in patients with renal impairment:

The clearance of allopurinol and oxypurinol is greatly reduced in patients with poor renal function resulting in higher plasma levels with chronic therapy. Patients with renal impairment, where creatinine clearance values were between 10 and 20 mL/min, showed plasma oxypurinol concentrations of approximately 30 mg/litre after prolonged treatment with 300 mg allopurinol per

day. This is approximately the concentration which would be achieved by doses of 600 mg/day in those with normal renal function. A reduction in the dose of MIRPOLYZ according to creatinine clearance is therefore required in patients with renal impairment (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The inactive ingredients are lactose monohydrate, maize starch, povidone, sodium starch glycollate, dried maize starch and micronized stearic acid.

MIRPOLYZ 300 mg tablets also contain a colourant: sunset yellow FCF aluminium lake (E110).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original packaging until required for use.

Keep blister strips in carton until required for use.

KEEP THIS MEDICINE OUT OF THE REACH OF CHILDREN.

6.5 Nature and contents of container

MIRPOLYZ tablets are packed in clear PVDC coated PVC/Aluminium foil blister strips of 7 or 10, which are further packed in printed cartons, in pack sizes of 28, 30 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dezzo Trading 392 (Pty) Ltd

Cnr. Jespan Centre, Corner Garrick

& Flagtail Street, Extension 8,

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8. REGISTRATION NUMBERS

MIRPOLYZ 100 mg tablets: 57/3.3/0017

MIRPOLYZ 300 mg tablets: 57/3.3/0018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06 September 2022

10. DATE OF REVISION OF THE TEXT