SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

PODAGRA OTC 0,5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0,5 mg colchicine.

Excipients with known effect:

Contains sugar: lactose monohydrate.

Each PODAGRA OTC tablet contains 50,80 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Round, white to pale yellow coloured tablets, plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PODAGRA OTC provides relief of acute attacks of gout in cases of emergency.

4.2 Posology and method of administration

Posology

Acute gout: the initial dose is 0,5 to 1 mg (1 to 2 tablets) by mouth, followed by 0,5 mg (1 tablet) every 2 hours until relief is obtained or gastrointestinal symptoms occur. The total dose usually required to alleviate an attack is 6 mg, and the latter amount should not be exceeded. The course should not be repeated within 3 days.

Method of administration

Tablets are taken orally

4.3 Contraindications

PODAGRA OTC is contraindicated in:

- Patients with a known hypersensitivity to colchicine or any of the ingredients in PODAGRA OTC listed in section 6.1.
- Patients with severe hepatic or renal insufficiency, who are taking a P-glycoprotein (P-gp) inhibitor or strong CYP3A4 inhibitor (see section 4.5).
- Patients with severe renal efficiency (creatinine clearance < 30 ml/min) or severe hepatic impairment.
- Use in combination with macrolide antibiotics (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- Patients undergoing haemodialysis since it cannot be removed by dialysis or exchange transfusion
- Patients with blood dyscrasias

4.4 Special warnings and precautions for use

Colchicine is potentially toxic so it is important not to exceed the dose (see section 4.2).

Colchicine has a narrow therapeutic window. The administration should be discontinued if toxic symptoms such as nausea, vomiting, abdominal pain, diarrhoea occur.

Colchicine may cause severe bone marrow depression (agranulocytosis, aplastic anaemia, thrombocytopenia). The change in blood counts may be gradual or very sudden. Aplastic anaemia in particular has a high mortality rate. Periodic checks of the blood picture are essential.

If patients develop signs or symptoms that could indicate a blood cell dyscrasia, such as fever, stomatitis, sore throat, prolonged bleeding, bruising or skin disorders, treatment with colchicine should be immediately discontinued and a full haematological investigation should be conducted straight away.

Caution is advised in case of:

• liver or renal impairment

• cardiovascular disease

• gastrointestinal disorders

• elderly and debilitated patients as there may be a greater risk of cumulative toxicity

• patients with abnormalities in blood counts

Patients with liver or renal impairment should be carefully monitored for adverse effects of colchicine (see section 5.2).

Co-administration with P-gp inhibitors and/or moderate or strong CYP3A4 inhibitors will increase the exposure to colchicine, which may lead to colchicine induced toxicity including fatalities. If treatment with a P-gp inhibitor or a moderate or strong CYP3A4 inhibitor is required in patients with normal renal and hepatic function, a reduction in colchicine dosage or interruption of colchicine treatment is recommended (see section 4.5).

It is recommended that concomitant treatment that may weaken renal/hepatic function and/or introduce bone marrow/muscular toxicity be assessed prior to initiating treatment with PODAGRA OTC.

Excipients: lactose intolerance

Contains lactose. Patients with the rare hereditary problems of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take PODAGRA OTC.

4.5 Interaction with other medicines and other forms of interaction

- Colchicine is a substrate for both CYP3A4 and the transport protein P-gp. In the presence of CYP3A4 or P-gp inhibitors, the concentrations of colchicine in the blood increase. Toxicity, including fatal cases, have been reported during concurrent use of CYP3A4 or P-gp inhibitors such as macrolides (azithromycin, clarithromycin, erythromycin and telithromycin), ciclosporin, ketoconazole, itraconazole, voriconazole, HIV protease inhibitors (e.g. ritonavir, atazanavir, indinavir), calcium channel blockers (verapamil and diltiazem) and disulfiram (see section 4.3 and section 4.4).
- PODAGRA OTC is contraindicated in patients with renal or hepatic impairment who are taking a P-gp inhibitor (e.g. ciclosporin, verapamil or quinidine) or a strong CYP3A4 inhibitor (e.g. ritonavir, atazanavir, indinavir, clarithromycin, telithromycin, itraconazole or ketaconazole) (see section 4.3).
- A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with a P-gp inhibitor or strong CYP3A4 inhibitor is required (see section 4.4).
- Caution is advised with concomitant administration of medicines that can affect the blood count or have a negative effect on hepatic and/or renal function.
- Medicines such as cimetidine and tolbutamide reduce metabolism of colchicine and thus plasma levels of colchicine increase.

- The consumption of grapefruit juice can cause colchicine toxicity due to the increase in plasma levels of PODAGRA OTC. Grapefruit juice should not be taken together with PODAGRA OTC.
- Blood dyscrasia-causing medicines (e.g. cytotoxic and immunosuppressive medicines, zidovudine, some sulphur-containing medicines [such as some Angiotensin-converting enzyme (ACE) inhibitors (e.g.captopril), co-trimoxazole, some antithyroid medicines], clozapine, penicillins, cephalosporins, anticonvulsants, diuretics, non-steroidal anti-inflammatory medicines (NSAIMS), sulfonamides, etc.) may intensify the leucopenic and/or thrombocytopenic effect of PODAGRA OTC with concurrent or recent use if these medications cause the same effects. Blood counts must be monitored if sequential or concurrent use cannot be avoided.
- Concomitant administration of PODAGRA OTC with HMG-CoA reductase inhibitors (atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin), fibrates, ciclosporin and digoxin may increase the risk of undesirable muscular effects especially myopathy and rhabdomyolysis.
- The absorption of Vitamin B12 may be impaired by chronic administration or high doses of PODAGRA OTC.

4.6 Fertility, pregnancy and lactation

Pregnancy

PODAGRA OTC is contraindicated in pregnancy (see section 4.3) as there may be a risk of foetal chromosome damage.

Breastfeeding

Colchicine is distributed in breast milk. Mothers on PODAGRA OTC should not breastfeed their infants.

Fertility

Colchicine administration in animals induces significant reductions in fertility.

4.7 Effects on ability to drive and use machines

The effects on the ability to drive and use machinery is not known. However, drowsiness and dizziness may occur. It is therefore recommended that patients experiencing these adverse reactions should not drive or use machines.

4.8 Undesirable effects

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Blood and lymphatic system disorders	-	Bone marrow suppression with agranulocytosis, thrombocytopenia, and aplastic anaemia.	-
Nervous system disorders	-	Peripheral neuritis, neuropathy.	-
Gastrointestinal disorders	Nausea, vomiting and diarrhoea, abdominal pain.	-	Profuse diarrhoea (large doses) and gastrointestinal haemorrhage.
Hepatobiliary disorders	-	-	Hepatic damage.
Skin and subcutaneous tissue disorders	-	-	Rashes (in large doses) and alopecia (during prolonged use).
Musculoskeletal and connective tissue disorders	-	Rhabdomyolysis, myopathy.	-

Renal and urinary disorders	-	-	Renal damage and dehydration (large doses).
Reproductive system and breast disorders	-	Azoospermia, amenorrhoea, dysmenorrhoea and oligospermia.	-

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 of overdose do not appear for at least several hours. The first symptoms are a feeling of burning and rawness in the mouth and throat and difficulty in swallowing. This is followed by nausea, vomiting and diarrhoea. The diarrhoea may be severe and haemorrhagic, and can lead to metabolic acidosis, dehydration and shock. A burning sensation of the throat, stomach and skin may also occur. Extensive vascular damage and acute renal toxicity with oliguria and haematuria may occur. Bone marrow depression with leucopenia may be followed by rebound leucocytosis. Multiple organ failure may occur and may manifest as CNS toxicity, bone marrow depression, hepatocellular damage, muscle damage, respiratory distress, myocardial injury and renal damage. The patient may develop convulsions, delirium, muscle weakness, neuropathy and ascending paralysis of the central nervous system. Death may be due to respiratory depression, cardiovascular collapse, bone marrow depression or sepsis. In surviving patients, alopecia, rebound leucocytosis and stomatitis may occur about 10 days after the acute overdose.

In case of overdose of acute poisoning; patients should be carefully monitored for some time to take account of the delayed onset of symptoms. In acute poisoning the stomach should be emptied by multiple dose activated charcoal administration. Treatment is symptomatic and supportive. Respiration may require assistance. The circulation and blood pressure should be maintained and fluid and electrolyte imbalances should be corrected. Haemodialysis or peritoneal dialysis may be of value when kidney function is compromised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class: A 3.3 Antigout preparations.

Pharmacotherapeutic group: Preparations with no effect on uric acid metabolism.

ATC Code: M04AC01

Colchicine is an anti-inflammatory medicine effective in the treatment of gout. An acute attack of gout occurs due to an inflammatory reaction to crystals of mono-sodium urate that are deposited in the joint tissue form hyperuric body fluids. The inflammatory response involves local infiltration of granulocytes that phagocytise the urate crystals. In synovial tissues and in leucocytes associated with the inflammatory process, lactic acid production is high and this favours a local decrease in pH that fosters further uric acid deposition. Colchicine diminishes lactic acid production by leucocytes directly and diminishes phagocytosis, which interrupts the cycle of urate crystal deposition and the inflammatory response that sustains the acute attack.

5.2 Pharmacokinetic properties

Absorption

Colchicine is well absorbed after oral administration. Peak plasma concentrations are reached 0,5 to 2 hours following administration.

Distribution

Plasma protein binding is 50 %. High concentrations of colchicine are found in the kidney, liver and spleen, it is however largely excluded from the heart, skeletal muscle and brain tissue.

Biotransformation

Colchicine undergoes significant enterohepatic circulation. Its metabolism may involve deacetylation in the liver. The plasma half-life of colchicine is approximately 9 hours.

Elimination

Most of the colchicine is excreted in faeces; however, in normal individuals 10 – 20 % of the colchicine is excreted in urine. In patients with liver disease, hepatic uptake and elimination are reduced and more colchicine may be excreted in urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone, pregelatinised starch, stearic acid, talc and lactose monohydrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

12 tablets in blister packs:

Store at or below 30 °C, in the original blister strip in the outer carton, until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

12 tablets in blister packs with strips of white opaque PA/aluminium/PVC film and 25µ aluminium foil of 6 or 12 tablets per blister strip. The blister strips are packed in cartons.

Not all packs or pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBER(S)

50/3.3/1036

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08 March 2022

10. DATE OF REVISION OF THE TEXT

02 September 2022