PROFESSIONAL INFORMATION

SCHEDULING STATUS: S2

1. NAME OF THE MEDICINE

GOUTEZE® OTC, 0,5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Contains 0,5 mg colchicine per tablet.

Contains sugar (50,80 mg lactose monohydrate per tablet).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GOUTEZE OTC is indicated for the relief of acute attacks of gout in cases of emergency.

4.2 Posology and method of administration

Posology

In acute gout the initial dose is 0,5 mg to 1 mg (1 to 2 tablets) immediately, followed by 0,5 mg (1 tablet) every 2 hours until pain is relieved or vomiting or diarrhoea intervenes.

A maximum total treatment course of 6 mg (12 tablets) should not be exceeded.

The course should not be repeated within 3 days, but preferably 7 days should elapse between courses of gout treatment with GOUTEZE OTC to avoid cumulative toxicity.

GOUTEZE OTC is not an analgesic medicine and should not be used to treat pain from other causes.

Special populations

Elderly

GOUTEZE OTC should be given with caution to the elderly (see section 4.4).

Paediatric population

There are no data available.

Method of administration

For oral use.

4.3 Contraindications

- Patients with known hypersensitivity to colchicine or any of the other ingredients of GOUTEZE OTC (see section 6.1).
- Patients with blood dyscrasias: myelosuppression, leukopenia, granulocytopenia, thrombocytopenia and aplastic anaemia.
- Patients with severe renal insufficiency (creatinine clearance < 30 ml/min).
- Patients undergoing haemodialysis since it cannot be removed by dialysis or exchange transfusion.
- Patients with severe hepatic insufficiency.
- Patients with renal or hepatic impairment who are taking P-glycoprotein (P-gp) inhibitors or potent CYP3A4 inhibitors (see section 4.5). In these patients, life-threatening and fatal colchicine toxicity has been reported with colchicine as in GOUTEZE OTC in therapeutic doses (see section 4.8).
- Combination with macrolide antibiotics and pristinamycin (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- Women of childbearing potential unless they are using effective contraceptive measures.

4.4 Special warnings and precautions for use

Fatal overdoses

GOUTEZE OTC is potentially toxic so it is important not to exceed the recommended dose as prescribed by a healthcare provider with the necessary knowledge and experience (see section 4.2). Colchicine, as contained in GOUTEZE OTC, has a narrow therapeutic window.

The administration should be discontinued if toxic symptoms such as nausea, vomiting, abdominal pain, diarrhoea occur (see sections 4.2 and 4.8). GOUTEZE OTC should be withdrawn, or the dose reduced if adverse gastrointestinal effects occur.

Fatal overdoses have been reported with colchicine, as contained in GOUTEZE OTC, in adults and children. Keep GOUTEZE OTC away from children.

GOUTEZE OTC should be given with great care to elderly or debilitated patients who may be particularly susceptible to cumulative toxicity and to those patients with cardiac, hepatic, renal or gastrointestinal disease. Patients with liver or renal impairment should be carefully monitored for adverse effects of colchicine as in GOUTEZE OTC.

Blood dyscrasias

GOUTEZE OTC should be avoided in patients with blood disorders (see section 4.3).

Colchicine, as contained in GOUTEZE OTC, 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 GOUTEZE OTC should be immediately discontinued and a full haematological investigation should be conducted straight away.

Hepatic and renal impairment

The dose should be reduced in patients with mild to moderate renal impairment. Patients with liver or renal impairment should be carefully monitored for adverse effects of GOUTEZE OTC and if present, consider temporary interruption or discontinuation of GOUTEZE OTC (see section 4.3).

Elderly population

GOUTEZE OTC should be given with care to old and debilitated patients and to those with cardiac, hepatic, renal or gastrointestinal disease.

P-gp inhibitors and/or moderate or strong CYP3A4 inhibitors

Co-administration of GOUTEZE OTC with P-gp inhibitors and/or moderate or strong CYP3A4 inhibitors will increase the exposure to GOUTEZE OTC, which may lead to GOUTEZE OTC 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 GOUTEZE OTC dosage or interruption of GOUTEZE OTC treatment is recommended (see section 4.5).

Excipients

GOUTEZE OTC contains lactose.

Patients with rare hereditary conditions of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take GOUTEZE OTC.

4.5 Interaction with other medicines and other forms of interaction

GOUTEZE OTC is contraindicated in patients with renal or hepatic impairment who are taking a P-glycoprotein inhibitor (e.g. ciclosporin, verapamil or quinidine) or a strong CYP3A4 inhibitor (e.g. ritonavir, atazanavir, indinavir, clarithromycin, telithromycin, itraconazole or ketoconazole) (see section 4.3 and 4.4).

Colchicine, as contained in GOUTEZE OTC, is a substrate for both the transport protein P-glycoprotein and the cytochrome P450 isoenzyme CYP3A4. 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 (clarithromycin, telithromycin and erythromycin, roxithromycin,), ciclosporin, ketoconazole, itraconazole, voriconazole, HIV protease inhibitors (ritonavir, atazanavir), calcium channel blockers (verapamil and diltiazem) and disulfiram (see sections 4.3 and 4.4).

A reduction in GOUTEZE OTC dosage or an interruption of treatment is recommended in patients with normal renal or hepatic function if treatment with a P-gp inhibitor or strong CYP3A4 inhibitor is required.

A 4-fold reduction in colchicine dosage is recommended when co-administered with a P-gp inhibitor (e.g., ciclosporin) and/or a strong CYP3A4 inhibitor (e.g., clarithromycin, ketoconazole, ritonavir). A 2-fold reduction in colchicine, as contained in GOUTEZE OTC dosage is recommended when co-administered with a moderate CYP3A4 inhibitor (e.g., verapamil, diltiazem, grapefruit juice (see sections 4.3 and 4.4)). Such combinations should be avoided in patients with renal and hepatic

impairment (see sections 4.3 and 4.4). Given the nature of the side effects, caution is advised with concomitant administration of medicine that can affect the blood count or have a negative effect on hepatic and/or renal function.

Pristinamycin

Concomitant administration may increase the side effects of GOUTEZE OTC with potentially fatal consequences (see section 4.3).

Oral anticoagulants

Concomitant administration of GOUTEZE OTC and oral anticoagulants may increase the effect of the oral anticoagulant and increase the risk of haemorrhage. More frequent INR checks are required. Possible modification of the dosage of the oral anticoagulant during treatment with GOUTEZE OTC and for 8 days after its cessation may be required.

Thiazide diuretics

Thiazide diuretics may increase serum uric acid levels and interfere with the activity of GOUTEZE OTC.

Cimetidine and tolbutamide

Cimetidine and tolbutamide reduce metabolism of colchicine and thus plasma levels of colchicine as contained in GOUTEZE OTC increase.

Grapefruit juice

Grapefruit juice may increase plasma levels of colchicine, as grapefruit juice is a moderate inhibitor of CYP3A4. Grapefruit juice should therefore not be taken together with colchicine as in GOUTEZE OTC.

Vitamin B_{12} (cyanocobalamin)

Reversible malabsorption of cyanocobalamin (vitamin B_{12}) may be induced by an altered function of the intestinal mucosa.

Statins (MHG-CoA inhibitors), fibrates, ciclosporin, digoxin

The risk of myopathy and rhabdomyolysis is increased by a combination of colchicine with statins, fibrates, ciclosporin or digoxin. Cases of myopathy, including rhabdomyolysis, have been reported with HMG-CoA reductase inhibitors and co-administration with GOUTEZE OTC, and caution should be exercised when given concomitantly. There may be an increased risk if renal function is impaired. Patients should be advised to report muscle pain or weakness.

Alcohol

Concomitant use of GOUTEZE OTC increases the risk of gastrointestinal disorders. Alcohol increases blood uric acid concentrations.

Non-steroidal anti-inflammatory medicines (NSAIDs)

Concomitant use may increase the risk of gastrointestinal symptoms or incidence of blood disorders.

Antineoplastic medicines

Cytolytic medicines may increase the serum uric acid concentrations.

Bone marrow depressants or radiation therapy

Additive bone marrow depression may occur and dosage reduction of GOUTEZE OTC may be required.

Medicines affecting the blood count, hepatic function or renal function

Given the nature of the side effects, 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have to use effective contraception during treatment (see section 4.3).

Pregnancy

GOUTEZE OTC is contraindicated in pregnancy due to animal teratogenicity and genotoxicity in vitro and in vivo and there are suggestions of a risk of foetal chromosome damage (see section 4.3).

Breastfeeding

Colchicine, as contained in GOUTEZE OTC, is distributed into breastmilk. Therefore, GOUTEZE OTC is contraindicated in women who are breastfeeding (see section 4.3).

Fertility

Colchicine administration in animals induces significant reductions in fertility.

4.7 Effects on ability to drive and use machines

GOUTEZE OTC is not expected to have an influence; however patients should not drive, use machinery or perform any tasks that require

concentration until they are certain that GOUTEZE OTC does not adversely affect their ability to do so safely (see section 4.8).

4.8 Undesirable effects

Summary of safety profile

Colchicine, contained in GOUTEZE OTC, frequently causes nausea, vomiting, abdominal pain and diarrhoea.

Tabulated list of adverse reactions

Blood and the lymphatic system disorders	
Frequency unknown:	Bone marrow suppression with agranulocytosis, thrombocytopenia, aplastic anaemia, leukopenia, neutropenia*
Nervous system disorders	
Frequency unknown:	Peripheral neuritis, peripheral neuropathy
Vascular disorders	
Frequency unknown:	Hypotension
Gastrointestinal disorders	
Frequent:	Nausea, vomiting, abdominal pain and diarrhoea** (see section 4.4)
Less frequent:	Burning of the throat
Frequency unknown:	Profuse diarrhoea, gastrointestinal haemorrhage
Hepatobiliary disorders	
Frequency unknown:	Hepatic damage, hepatotoxicity

Skin and subcutaneous tissue disorders	
Less frequent:	Urticaria, morbilliform eruptions
Frequency unknown:	Burning of the skin and skin rashes, alopecia
Musculoskeletal, connective tissue and bone disorders	
Frequency unknown:	Myopathy, rhabdomyolysis
Renal and urinary disorders	
Frequency unknown:	Renal damage and dehydration
Reproductive system and breast disorders	
Frequency unknown:	Amenorrhoea, dysmenorrhoea, oligospermia, reversible azoospermia

Description of selected adverse reactions

* Larger doses may cause profuse diarrhoea, gastrointestinal haemorrhage, skin rashes and renal damage. Bone marrow depression with agranulocytosis, thrombocytopenia and aplastic anaemia have occurred on prolonged treatment, as well as peripheral neuritis, myopathy, rashes and alopecia.

** GOUTEZE OTC should be withdrawn or the dose reduced if gastrointestinal side effects occur.

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 providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: **https://www.sahpra.org.za/Publications/Index/8**.

4.9 Overdose

Colchicine has a narrow therapeutic window and is extremely toxic in overdose, it has been associated with serious and fatal toxicity. Patients at particular risk of toxicity are those with renal or hepatic impairment, gastrointestinal or cardiac disease, and patients at extremes of age (very young and very old). Following colchicine overdose, all patients, even in the absence of early symptoms, should be referred for immediate medical assessment (see section 4.4).

Symptoms

There is often a delay of up to 6 hours before toxicity is apparent; some features may be delayed up to 1 week or longer. Early symptoms of acute overdosage may be delayed (which occur up to 1 day after ingestion but 3 hours on average): nausea, vomiting, abdominal pain, haemorrhagic gastroenteritis, volume depletion, electrolyte abnormalities, diarrhoea, electrolyte disturbances, hypovolaemic shock, leukocytosis, hypotension in severe cases.

The second phase with life-threatening complications develops 24 to 72 hours (7 days or longer) after medicine administration: hepatic impairment, hyperpyrexia, bone marrow depression with leukopenia followed by rebound leukocytosis, multisystem organ dysfunction, acute renal failure, confusion, coma, ascending peripheral motor and sensory neuropathy, myocardial depression (decreased cardiac output), pancytopenia, cardiac dysrhythmias, respiratory failure (respiratory distress), consumption coagulopathy. A toxic epidermal necrolysis-like reaction has also been reported. These can progress in severe cases to multiple organ damage with bone marrow aplasia, convulsions, coma, delirium, rhabdomyolysis,

neuropathy, hepatocellular damage and ascending paralysis of the central nervous system, disseminated intravascular coagulation and death. Death is usually a result of respiratory depression and cardiovascular collapse. If the patient survives, recovery may be accompanied by rebound leukocytosis and reversible alopecia starting about one week after the initial ingestion. The lethal dose varies widely (7 mg to 65 mg single dose) for adults but is generally about 20 mg.

Treatment

No antidote is available. In acute overdosage, the value of gut decontamination is uncertain. Consider oral activated charcoal 50 g in adults who have ingested more than 0,1 mg/kg bodyweight within 1 hour of presentation and children who have ingested any amount of GOUTEZE OTC within 1 hour may be given activated charcoal 1 g/kg. Doses may be repeated every 4 hours in both adults and children, for those who have ingested more than 300 µg/kg, provided they are not vomiting. Haemodialysis and haemoperfusion has no efficacy (high apparent distribution volume) as they do not enhance GOUTEZE OTC elimination; blood and urine concentrations are of no use diagnostically (see section 4.3).

Close clinical and biological monitored are required in a hospital environment. Management is mainly symptomatic and supportive, with attention given to respiration, pulse, blood pressure and circulation, and cardiac rhythm; fluid and electrolyte imbalances should be corrected.

In cases of overdosage or acute poisoning patients should be carefully monitored. Patients are monitored for at least 6 hours after ingestion, or 12 hours if they have taken more than 300 µg/kg. Asymptomatic patients

may then be discharged, with advice to return if gastrointestinal symptoms appear.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 3.3 Anti-gout preparations

Pharmacotherapeutic group: Preparations with no effect on uric acid metabolism. ATC code: M04AC01

Colchicine is an anti-inflammatory medicine, effective against gout.

An acute attack of gout apparently occurs as a result of an inflammatory reaction to crystals of mono-sodium urate that are deposited in the joint tissue from 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 by diminishing phagocytosis, and thereby interrupts the cycle of urate crystal deposition and inflammatory response that sustains the acute attack.

5.2 Pharmacokinetic properties

Absorption

Colchicine is well absorbed after oral administration. Peak plasma concentration appears between 0,5 and 2 hours after administration.

Distribution

Plasma protein binding is 50 %. The formation of colchicine-tubulin complexes in many tissues contributes to its large volume of distribution. There is significant enterohepatic circulation. High concentrations of colchicine are observed in the kidney, liver and spleen, but it is largely excluded from heart, skeletal muscle and brain tissue.

Biotransformation

The exact metabolism of colchicine in humans is unknown, but *in vitro* studies indicate that it may undergo oxidative demethylation by CYP3A4. Metabolism may involve deacetylation in the liver. The plasma half-life is about 9 hours. Other CYP3A4 substrates have been associated with an increase in colchicine plasma t½ and the emergence of colchicine toxicity.

Elimination

In normal individuals 10-20 % of the medicine is excreted in urine. In patients with liver disease, hepatic uptake and elimination are reduced and more colchicine is excreted in the urine. The plasma t½ of colchicine is approximately 9 hours, but colchicine can be detected in leukocytes and in the urine for at least 9 days after a single intravenous dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Pregelatinised starch

Stearic acid

Talc

Povidone

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C in the original packaging.

Keep blisters in the carton until required for use.

6.5 Nature and contents of container

GOUTEZE OTC tablets are packed in a cardboard carton containing silver

OPA/Al/PVC - Aluminium foil blisters with 6 or 12 tablets.

Not all pack sizes may necessarily be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Abex Pharmaceutica (Pty) Ltd

Suite C, Rubenstein Ridge

617 Rubenstein Drive

Moreleta Park, 0181

South Africa

8. REGISTRATION NUMBER(S)

GOUTEZE OTC: 51/3.3/0358

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 June 2018

10. DATE OF REVISION OF THE TEXT

14 December 2023