PROFESSIONAL INFORMATION

SCHEDULING STATUS

S2

1 NAME OF MEDICINE
GOUTACK 0,5 mg 0,5 mg (Tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 0,5 mg colchicine.

Excipient with known effect:
Each tablet contains 50,85 mg lactose monohydrate equivalent to 48,31 mg lactose (see section 4.4).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.
A 5,5 mm, round shallow biconvex white tablet, plain on both sides.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
GOUTACK 0,5 mg 0,5 mg is indicated for the relief of acute attacks of gout in cases of emergency.

4.2 Posology and method of administration
Posology
Adults
In acute gout the initial dose is 0,5 mg to 1 mg (i.e., 1 to 2 tablets) by mouth immediately, followed by 0,5 mg (1 tablet) every 2 hours until pain relief is obtained or gastrointestinal symptoms such as vomiting, or diarrhoea occur.

A maximum total treatment course of 6 mg must not be exceeded. The course should not be repeated within 3 days, but preferably 7 days should elapse between courses of gout treatment with GOUTACK 0,5 mg 0,5 mg to avoid cumulative toxicity.

GOUTACK 0,5 mg 0,5 mg is not an analgesic medicine and should not be used to treat pain from other causes.

Special populations
Elderly
GOUTACK 0,5 mg 0,5 mg should be used with caution in the elderly.

Paediatric populations
Safety and efficacy of GOUTACK 0,5 mg 0,5 mg have not been established in paediatric populations.

Method of administration
Oral route.
Tablet should be swallowed with a glass of water.

4.3 Contraindications
GOUTACK 0,5 mg 0,5 mg is contraindicated in:
- Patients with hypersensitivity to colchicine or to any of the excipients (see section 6.1);
- Pregnancy and lactation (see section 4.6);
- Patients with serious gastrointestinal, renal, hepatic or cardiac disorders (see section 4.4);
- Patients with blood dyscrasias: myelosuppression, leukopenia, granulocytopenia, thrombocytopenia and aplastic anaemia (see section 4.4).
- Women of childbearing potential unless they are using effective contraceptive measures.
- Patients with severe renal impairment (creatinine clearance < 30 mL/min) .
- Patients with severe hepatic impairment.
- Patients undergoing haemodialysis since it cannot be removed by dialysis or exchange transfusion.
- Patients with renal or hepatic impairment who are taking a P-glycoprotein (P-gp) inhibitor or a strong CYP3A4 inhibitor (see section 4.5). In these patients, life-threatening and fatal colchicine toxicity has been reported with GOUTACK 0,5 mg 0,5 mg in therapeutic doses.
- Combination with macrolide antibiotics and pristinamycin.

4.4 Special warnings and precautions for use
Fatal overdoses
GOUTACK 0,5 mg 0,5 mg 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 GOUTACK 0,5 mg 0,5 mg, 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). GOUTACK 0,5 mg 0,5 mg should be withdrawn or the dose reduced if adverse gastrointestinal effects occur. Fatal overdoses have been reported with colchicine, as contained in GOUTACK 0,5 mg 0,5 mg, in adults and children. Keep GOUTACK 0,5 mg 0,5 mg away from children. GOUTACK 0,5 mg 0,5 mg should be given with great care to elderly or debilitated patients who may be particularly susceptible to cumulative toxicity and to those patients with cardiovascular, hepatic, renal or gastrointestinal disease. Patients with liver or renal impairment should be carefully monitored for adverse effects of colchicine.

Blood dyscrasias
Colchicine, as contained in GOUTACK 0,5 mg 0,5 mg, 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 (see section 4.3). 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 GOUTACK 0,5 mg 0,5 mg should be immediately discontinued and a full haematological investigation should be conducted straight away.

Hepatic and renal impairment
Patients with liver or renal impairment should be carefully monitored for adverse effects of GOUTACK 0,5 mg 0,5 mg (see sections 4.2, 4.3 and 4.8). Co-administration with P-gp inhibitors and/or moderate or strong CYP3A4 inhibitors will increase the exposure to colchicine, as contained in GOUTACK 0,5 mg 0,5 mg, 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 GOUTACK 0,5 mg 0,5 mg dosage or interruption of GOUTACK 0,5 mg 0,5 mg treatment is recommended (see sections 4.3 and 4.5).

Elderly
GOUTACK 0,5 mg 0,5 mg should be given with care to old and debilitated patients and to those with cardiac, hepatic, renal or gastrointestinal disease.

Co-administration with P-gp inhibitors and/or moderate or strong CYP3A4 inhibitors
Co-administration with P-gp inhibitors and/or moderate or strong CYP3A4 inhibitors will increase the exposure to GOUTACK 0,5 mg 0,5 mg, which may lead to GOUTACK 0,5 mg 0,5 mg 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 GOUTACK 0,5 mg 0,5 mg dosage or interruption of GOUTACK 0,5 mg 0,5 mg treatment is recommended (see sections 4.3 and 4.8).

Paediatric population
Safety and efficacy of GOUTACK 0,5 mg 0,5 mg have not been established in paediatric populations.

Excipients
GOUTACK 0,5 mg 0,5 mg contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take GOUTACK 0,5 mg 0,5 mg.

4.5 Interaction with other medicines and other forms of interaction
GOUTACK 0,5 mg 0,5 mg 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 ketoconazole) (see section 4.3). Colchicine, as contained in GOUTACK 0,5 mg 0,5 mg, 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 (clarithromycin, telithromycin and erythromycin), 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 GOUTACK 0,5 mg 0,5 mg 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 GOUTACK 0,5 mg 0,5 mg 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 of pristinamycin and GOUTACK 0,5 mg 0,5 mg can increase the undesirable effects of colchicine with potentially fatal consequences (see section 4.3)

Oral anticoagulants
Concomitant administration of GOUTACK 0,5 mg 0,5 mg 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 GOUTACK 0,5 mg 0,5 mg and for 8 days after its cessation may be required.

Thiazide diuretics
May increase serum uric levels and interfere with the activity of GOUTACK 0,5 mg 0,5 mg.

Cimetidine and tolbutamide
Reduce metabolism of colchicine and thus plasma levels of GOUTACK 0,5 mg 0,5 mg increase.

Grapefruit juice
May increase plasma levels of GOUTACK 0,5 mg 0,5 mg as grapefruit juice is a moderate inhibitor of CYP3A4. Grapefruit juice should therefore not be taken together with GOUTACK 0,5 mg 0,5 mg.

Vitamin B12 (cyanocobalamin)
Reversible malabsorption of cyanocobalamin (vitamin B12) may be induced by an altered function of the intestinal mucosa.

Statins (HMG-CoA reductase 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 GOUTACK 0,5 mg 0,5 mg, 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 GOUTACK 0,5 mg 0,5 mg increases the risk of gastrointestinal disorders. Alcohol increases blood uric acid concentrations.

Non-steroidal anti-inflammatory drugs (NSAIDs)
Concomitant use may increase the risk of gastrointestinal symptoms.

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 GOUTACK 0,5 mg 0,5 mg 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 must use effective contraception during treatment with GOUTACK 0,5 mg 0,5 mg.

Pregnancy
GOUTACK 0,5 mg 0,5 mg should not be used during pregnancy.

Breastfeeding
Colchicine may be excreted in breast milk. GOUTACK 0,5 mg 0,5 mg should not be given to lactating mothers because of the risk of cytotoxic effects.

Fertility
No data is available.

4.7 Effects on ability to drive and use machines
GOUTACK 0,5 mg 0,5 mg 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 GOUTACK 0,5 mg 0,5 mg do not adversely affect their ability to do so safely (see section 4.8).

4.8 Undesirable effects
a. Tabulated summary of adverse reactions

System Organ Class	Frequency	Undesirable effect
Blood and lymphatic system disorders	Frequency Unknown	Bone marrow depression with agranulocytosis, aplastic anaemia, leukopenia, thrombocytopenia, neutropenia*
Nervous system disorders	Frequency Unknown	Peripheral neuritis, peripheral neuropathy
Vascular disorders	Frequency Unknown	General vascular damage, hypotension (with large doses)
Immune system disorders	Frequency Unknown	Hypersensitivity reactions
Gastrointestinal system disorders	Frequent	Abdominal pain, nausea, vomiting and diarrhoea**
	Less Frequent	Burning of the throat
	Frequency Unknown	Gastrointestinal haemorrhage, profuse diarrhoea
Hepatobiliary disorders	Frequency Unknown	Hepatotoxicity, hepatic damage
Skin and subcutaneous tissue disorders	Less Frequent	Urticaria, morbilliform eruptions
	Frequency Unknown	Alopecia, skin rashes, vesicular dermatitis, purpura and dermatoses, burning of the skin
Musculoskeletal and connective tissue disorders	Frequency Unknown	Myopathy, joint pain, rhabdomyolysis
Renal and urinary disorders	Frequency Unknown	Renal damage, anuria, haematuria, oliguria, dehydration
Reproductive system and breast disorders	Frequency Unknown	Amenorrhoea, dysmenorrhoea, oligospermia, reversible azoospermia

b. 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.
** GOUTACK 0,5 mg 0,5 mg should be withdrawn or the dose reduced if gastrointestinal side effects occur.

c. 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 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
Symptoms
Colchicine, as contained in GOUTACK 0,5 mg 0,5 mg, 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).

Clinical
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, leucocytosis, 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 leucocytosis, 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 leucocytosis 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 GOUTACK 0,5 mg 0,5 mg 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 GOUTACK 0,5 mg 0,5 mg elimination; blood and urine concentrations are of no use diagnostically (see section 4.3).

Close clinical and biological monitoring in 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
A. 3.3 Antigout Preparations
Pharmacotherapeutic group: Preparations with no effect on uric acid metabolism
ATC code: M04AC01

Colchicine is an anti-inflammatory medicine unique in its selective effectiveness 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 or granulocytes that phagocytize the urate crystals. In synovial tissues an 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.

Colchicine is not an analgesic, although it relieves pain in acute attacks. It is not a uricosuric medicine and will not prevent the progression of gout to chronic gouty arthritis. It has a prophylactic, suppressive effect which helps reduce the incidence of acute attacks and relieve the patient's occasional residual pain and mild discomfort.

Colchicine can produce a temporary leukopenia which is followed by leucocytosis.

5.2 Pharmacokinetic properties
Absorption
Colchicine is rapidly, but variable absorbed after oral administration. Peak plasma concentrations are seen between 0,5 to 2 hours after administration.

Distribution
Plasma half-life about 1 hour, but 60 hours in leucocytes, which is increased in renal function impairment and decreased in hepatic function impairment
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 seen in the kidney, liver, and spleen, but it apparently is largely excluded from heart, skeletal muscle and brain tissue.
Colchicine does not appear to be specifically localised in any tissues except the liver leucocytes, spleen and kidneys; it undergoes enterohepatic circulation.

Biotransformation
Deacetylated in the liver.

Elimination
Colchicine is mainly excreted in the faeces. Urinary excretion is 10 % to 20 % but increases with liver disease. The plasma $t_{½}$ 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.

5.3 Preclinical safety data
Colchicine has been shown to be teratogenic in animals and there is a risk of teratogenicity or of foetal damage in humans.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose monohydrate
Maize starch
Magnesium stearate
Pre-gelatinised starch

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store at or below 25 ºC.

6.5 Nature and contents of container
High Density Polyethylene (HDPE) containers with polypropylene caps containing 12,100 or 500 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 HOLDERS OF CERTIFICATE OF REGISTRATION
Trinity Pharma (Pty) Ltd.
3 Gwen Lane, 4th Floor, Sandton, Gauteng, 2031.

8 REGISTRATION NUMBER
55/3.3/0336

9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION
28 February 2023

10 DATE OF REVISION OF THE TEXT
N.A

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