PROFESSIONAL INFORMATION

SCHEDULING STATUS

S2

1 NAME OF MEDICINE

COLCHICINE 0,5 mg TRINITY (Tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0,5 mg colchicine.

Excipient with known effect:

Contains sugar: 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

COLCHICINE 0,5 mg TRINITY 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 COLCHICINE 0,5 mg TRINITY to avoid cumulative toxicity.

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

Special populations

Elderly

COLCHICINE 0,5 mg TRINITY should be used with caution in the elderly.

Paediatric populations

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

Method of administration

Oral route.

Tablet should be swallowed with a glass of water.

4.3 Contraindications

COLCHICINE 0,5 mg TRINITY 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 COLCHICINE 0,5 mg TRINITY in therapeutic doses.
- Combination with macrolide antibiotics and pristinamycin.

4.4 Special warnings and precautions for use

Fatal overdoses

COLCHICINE 0,5 mg TRINITY 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 COLCHICINE 0,5 mg TRINITY, 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). COLCHICINE 0,5 mg TRINITY should be withdrawn or the dose reduced if adverse gastrointestinal effects occur. Fatal overdoses have been reported with colchicine, as contained in COLCHICINE 0,5 mg TRINITY, in adults and children. Keep COLCHICINE 0,5 mg TRINITY away from children. COLCHICINE 0,5 mg TRINITY 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 COLCHICINE 0,5 mg TRINITY, 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 COLCHICINE 0,5 mg TRINITY 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 COLCHICINE 0,5 mg TRINITY (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 COLCHICINE 0,5 mg TRINITY, 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 0,5 mg TRINITY dosage or interruption of COLCHICINE 0,5 mg TRINITY treatment is recommended (see sections 4.3 and 4.5).

Elderly population

COLCHICINE 0,5 mg TRINITY 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 COLCHICINE 0,5 mg TRINITY, which may lead to COLCHICINE 0,5 mg TRINITY 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 0,5 mg TRINITY dosage or interruption of COLCHICINE 0,5 mg TRINITY treatment is recommended (see sections 4.3 and 4.8).

Paediatric population

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

Excipients

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

4.5 Interaction with other medicines and other forms of interaction

COLCHICINE 0,5 mg TRINITY 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 COLCHICINE 0,5 mg TRINITY, 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 COLCHICINE 0,5 mg TRINITY 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 COLCHICINE 0,5 mg TRINITY 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 COLCHICINE 0,5 mg TRINITY can increase the undesirable effects of colchicine with potentially fatal consequences (see section 4.3)

Oral anticoagulants

Concomitant administration of COLCHICINE 0,5 mg TRINITY 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 COLCHICINE 0,5 mg TRINITY and for 8 days after its cessation may be required.

Thiazide diuretics

May increase serum uric levels and interfere with the activity of COLCHICINE 0,5 mg TRINITY.

Cimetidine and tolbutamide

Reduce metabolism of colchicine and thus plasma levels of COLCHICINE 0,5 mg TRINITY increase.

Grapefruit juice

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

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 COLCHICINE 0,5 mg TRINITY, 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 COLCHICINE 0,5 mg TRINITY 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 COLCHICINE 0,5 mg TRINITY 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 COLCHICINE 0,5 mg TRINITY.

Pregnancy

COLCHICINE 0,5 mg TRINITY should not be used during pregnancy.

Breastfeeding

Colchicine may be excreted in breast milk.

Fertility

No data is available.

4.7 Effects on ability to drive and use machines

COLCHICINE 0,5 mg TRINITY 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 COLCHICINE 0,5 mg TRINITY 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, aplastic anaemia, leukopenia, 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.

** COLCHICINE 0,5 mg TRINITY 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 COLCHICINE 0,5 mg TRINITY, 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, hemorrhagic 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. Gastric lavage may be an alternative in adults who present within 1 hour of a potentially, acute life-threatening overdose. 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 COLCHICINE 0,5 mg TRINITY 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 COLCHICINE 0,5 mg TRINITY 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 agent 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 agent 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 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.

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1686

8 REGISTRATION NUMBER(S)

55/3.3/0336

9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

28 February 2023

10 DATE OF REVISION OF THE TEXT

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