PROFESSIONAL INFORMATION

COLCHICINE 0,5 mg ACTIVO

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

COLCHICINE 0,5 mg ACTIVO, tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each COLCHICINE 0,5 mg ACTIVO tablet contains 0,5 mg colchicine.

COLCHICINE 0,5 mg ACTIVO contains sugar: 50,80 mg lactose monohydrate per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

COLCHICINE 0,5 mg ACTIVO tablets are round, white to pale yellow coloured tablets and plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COLCHICINE 0,5 mg ACTIVO is indicated for relief of acute attacks of gout in cases of emergency.

4.2 Posology and method of administration

Posology

Acute attacks of gout in adult patients:

The initial dose is 0,5 mg to 1 mg (1 to 2 tablets) by mouth immediately, followed by 0,5 mg (1 tablet) 2 hourly until pain is relieved or until vomiting or diarrhoea occur.

The maximum total treatment course of 6 mg (twelve tablets) 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 ACTIVO to avoid cumulative toxicity.

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

Special populations

Elderly:

COLCHICINE 0,5 mg ACTIVO should be given with caution to the elderly (see section 4.4).

Paediatric population

There are no data available.

Method of administration

COLCHICINE 0,5 mg ACTIVO is for oral administration.

4.3 Contraindications

COLCHICINE 0,5 mg ACTIVO is contraindicated in:

- patients with known hypersensitivity to the active substance (colchicine) or to any of the excipients listed in section 6.1.
- patients undergoing haemodialysis since COLCHICINE 0,5 mg ACTIVO cannot be removed by dialysis or exchange transfusion.
- patients with severe renal impairment (creatinine clearance less than 30 ml/minute).

- patients with severe hepatic impairment.
- patients with renal or hepatic impairment should not be given COLCHICINE 0,5 mg ACTIVO in conjunction with P-glycoprotein (P-gp) inhibitors (e.g ciclosporin, verapamil or quinidine) or potent CYP3A4 inhibitors (e.g. ritonavir, atazanavir, indinavir, clarithromycin, telithromycin, itraconazole or ketoconazole). In these patients, life-threatening and fatal colchicine toxicity has been reported. (see section 4.4 and 4.5).
- combination with macrolide antibiotics and pristinamycin.
- patients with blood disorders: myelosupression, leucopenia, granulocytopenia, thrombocytopenia and aplastic anaemia.
- pregnancy and lactation.
- women of childbearing potential unless they are using effective contraceptive measures.

4.4 Special warnings and precautions for use

Colchicine is potentially toxic so it is important not to exceed the dose prescribed by a healthcare professional with the necessary knowledge and experience.

Colchicine has a narrow therapeutic window. The administration should be discontinued if toxic symptoms such as nausea, vomiting, abdominal pain, diarrhoea occur. COLCHICINE 0,5 mg ACTIVO should be withdrawn or the dose reduced if adverse gastrointestinal effects occur.

Fatal overdoses

Fatal overdoses have been reported with colchicine in adults and children. Keep COLCHICINE 0,5 mg ACTIVO away from children. COLCHICINE 0,5 MG ACTIVO 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. Monitor for toxicity and if present consider temporary interruption or discontinuation of COLCHICINE 0,5 mg ACTIVO (see section 4.3).

Blood dyscrasias

Colchicine may cause severe bone marrow depression (agranulocytosis, aplastic anaemia, thrombocytopenia). Myelosupression, leucopenia and granulocytopenia have also been reported (see section 4.3). 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.

P-gp and/or CYP3A4 inhibitor interactions

Coadministration of COLCHICINE 0,5 mg ACTIVO with moderate or strong CYP3A4 inhibitors will increase the exposure of colchicine and may result in life-threatening interactions, colchicine induced toxicity including fatalities (see section 4.5). 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).

Neuromuscular toxicity

Myotoxicity including rhabdomyolysis may occur, especially in combination with other medicines known to cause this effect. Concomitant administration of COLCHICINE 0,5 mg ACTIVO with medicines such as ciclosporin and HMG-CoA reductase inhibitors (e.g. simvastatin) may increase the undesirable effects of COLCHICINE 0,5 mg ACTIVO. Clinical and biological monitoring (measurement of creatinine kinase) is required. Do not exceed several days of treatment with COLCHICINE 0,5 mg ACTIVO (see section 4.5).

Information about excipients

COLCHICINE 0,5 mg ACTIVO contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, total lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take COLCHICINE 0,5 mg ACTIVO.

4.5 Interaction with other medicines and other forms of interaction

P-glycoprotein (P-gp) or strong CYP3A4 inhibitors:

COLCHICINE 0,5 MG ACTIVO 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 is a substrate for P-glycoprotein and the cytochrome P450 isoenzyme CYP3A4. Inhibitors of these may increase COLCHICINE 0,5 mg ACTIVO blood concentrations and the potential for toxicity. Life-threatening or fatal interactions have been reported when COLCHICINE 0,5 mg ACTIVO was given with macrolides (such as clarithromycin, erythromycin, telithromycin), ciclosporin, HIV protease inhibitors (such as ritonavir, atazanavir, indinavir), itraconazole, ketoconazole or calcium channel antagonists (such as verapamil and diltiazem) and disulfiram. If treatment with a P-glycoprotein inhibitor (e.g. digoxin), CYP3A4 inhibitors, or HIV-protease inhibitors is required in patients with normal renal and hepatic function, the COLCHICINE 0,5 mg ACTIVO dose may need to be reduced or an interruption of treatment is recommended. 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 ACTIVO 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 or hepatic impairment (see section 4.3). 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 ACTIVO can increase the undesirable effects of colchicine with potentially fatal consequences (see section 4.3).

Alcohol: Concomitant use of COLCHICINE 0,5 mg ACTIVO 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.

Oral anticoagulants: Concomitant administration may increase the effect of the oral anticoagulant, such as warfarin, and increase the risk of haemorrhage. More frequent INR checks are required. Possible modification of the dosage of the oral anticoagulant during COLCHICINE 0,5 mg ACTIVO treatment and for 8 days after its cessation may be required.

Blood dyscrasia-causing medications e.g. chloramphenicol, co-trimoxazole, clozapine, olanzapine, carbimazole, lamotrigine, phenytoin, valproic acid, carbamazepine: The leucopenic and/or thrombocytopenic effects of COLCHICINE 0,5 mg ACTIVO may be intensified with concurrent or recent therapy if these medicines cause the same effects. Examples of medicines causing blood dyscrasias are certain antibiotics e.g. chloramphenicol and cotrimoxazole, anti-psychotics e.g. clozapine and olanzapine, anti-thyroid medicines e.g. carbimazole and anti-epileptics e.g. lamotrigine, phenytoin, valproic acid and carbamazepine. Blood counts should be monitored if concurrent or sequential use cannot be avoided.

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 ACTIVO may be required.

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

HMG-CoA reductase inhibitors (Statins), 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, 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.

Thiazide diuretics: May increase serum uric acid and interfere with the activity of COLCHICINE 0,5 mg ACTIVO.

In addition, substances such as cimetidine and tolbutamide reduce metabolism of colchicine and thus plasma levels of colchicine increase.

Grapefruit juice may increase plasma levels of colchicine as it is a moderate inhibitor of CYP3A4. Grapefruit juice should therefore not be taken together with colchicine.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and female

Women of childbearing potential have to use effective contraception during treatment.

Pregnancy

The use of COLCHICINE 0,5 mg ACTIVO is contraindicated in pregnancy as it is known to be genotoxic *in vitro* and *in vivo* and is teratogenic in animals and there are suggestions of a risk of foetal chromosome damage.

Breastfeeding

Colchicine is excreted in breast milk. Therefore, use of COLCHICINE 0,5 mg ACTIVO 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

COLCHICINE 0,5 mg ACTIVO is not expected to adversely affect the ability to drive or operate machinery safely (see section 4.8). The patient should however determine how COLCHICINE 0,5 mg ACTIVO affects him/her before judging whether it is safe to drive or operate machinery. If there is any doubt, the patient should discuss this with a healthcare provider.

4.8 Undesirable effects

Summary of safety profile

Colchicine frequently causes nausea, vomiting, abdominal pain and diarrhoea.

Tabulated list of adverse reactions

Blood and lymphatic system disorders:

Frequency unknown:	Bone marrow depression with agranulocytosis, thrombocytopenia, aplastic anaemia, leucopenia, neutropenia*

Nervous system disorders:

Frequency unknown:	Peripheral neuritis, peripheral neuropathy

Vascular disorders:

Frequency unknown:	Hypotension (large doses)

Gastrointestinal disorders:

Frequent:	Nausea, vomiting, abdominal pain and diarrhoea COLCHICINE 0,5 mg ACTIVO should be withdrawn or the dose reduced if gastrointestinal side effects occur.
Less frequent:	Burning of throat
Frequency unknown:	Profuse diarrhoea, gastrointestinal haemorrhage

Hepatobiliary disorders:

Frequency unknown:	Hepatic damage, hepatoxicity

Skin and subcutaneous tissue disorders:

Less frequent:	Urticaria, morbilliform eruptions
Frequency unknown:	Burning of the skin, skin rashes, alopecia

Musculoskeletal, connective tissue and bone disorders:

Frequency unknown:	Myopathy, rhabdomyolysis

Renal and urinary disorders:

Frequency unknown: Renal damage, dehydration (large doses)

Reproductive system and breast disorders:

Frequency unknown: Azoospermia, reversible upon cessation of treatment, amenorrhoea, dysmenorrhoea, oligospermia

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.

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

COLCHICINE 0,5 mg ACTIVO has a narrow therapeutic index 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 the very young or very old.

Following overdose, all patients, even in the absence of early symptoms, should be referred for immediate medical assessment.

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) include nausea, vomiting, abdominal pain, haemorrhagic gastroenteritis, volume depletion, electrolyte abnormalities, diarrhoea, electrolyte disturbances, hypovolaemic shock, leukocytosis, and hypotension in severe cases. Diarrhoea may be profuse and bloody, causing electrolyte disturbances and hypovolaemic shock. A burning sensation of the throat, stomach and skin may occur. Extensive vascular damage and acute renal toxicity with oliguria and haematuria have been reported.

The second phase with life threatening complications develops 24 to 72 hours (7 days or longer) after medicine administration include confusion, decreased cardiac output, cardiac dysrhythmias, renal and hepatic impairment, respiratory distress, hyperpyrexia, and bone marrow depression with leucopenia followed by rebound leucocytosis, multisystem organ dysfunction, ascending peripheral motor and sensory neuropathy, pancytopenia and consumption coagulopathy. These can progress in severe cases to multiple organ damage with bone marrow aplasia, convulsions, delirium coma, rhabdomyolysis, neuropathy, hepatocellular damage, and ascending paralysis of the CNS (central nervous system) and 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. A toxic epidermal necrolysis-like reaction has also been reported. 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. Oral activated charcoal 50 g can be considered for adults who ingested more than 100 µg/kg within 1 hour of presentation; children who have ingested any amount of COLCHICINE 0,5 mg ACTIVO 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 ingested more than 300 µg/kg, provided they are not vomiting. Management is mainly symptomatic and supportive, with attention given to respiration, pulse, blood pressure, circulation and cardiac rhythm; fluid and electrolyte imbalances should be corrected. In cases of overdosage or acute poisoning, patients should be carefully monitored.

Patients should be 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. Haemodialysis and haemoperfusion are of no benefit (high apparent distribution volume) as they do not enhance COLCHICINE 0,5 mg ACTIVO elimination (see section 4.3). Blood and urine concentrations are of no use diagnostically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 3.3 Antigout preparations.

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

ATC: M04AC01.

Mechanism of action:

Colchicine is an anti-inflammatory medicine which diminishes lactic acid production by leucocytes directly and diminishes phagocytosis. It is considered to act against the inflammatory response to urate crystals, by possibly inhibiting the migration of granulocytes into the inflamed area. Other properties of colchicine, such as interaction with the microtubules, could also contribute to the operation.

Onset of action is approximately 12 hours after oral administration and is maximal after 1 to 2 days.

5.2 Pharmacokinetic properties

Absorption

Colchicine is rapidly and almost completely absorbed after oral administration. Peak plasma concentrations occur 0,5 to 2 hours after dosing. The terminal half-life is 3 to 10 hours.

Distribution

In plasma, 50 % of colchicine is protein bound. The formation of colchicine-tubulin complexes in many tissues contributes to its large volume of distribution. There is significant enterohepatic circulation. The kidney, liver and spleen also contain high concentrations of colchicine, but it apparently is largely excluded from heart, skeletal muscle and brain.

Biotransformation

Colchicine is partially metabolised in the liver and then in part via the bile. It accumulates in leucocytes. The exact metabolism of colchicine in humans is unknown, but in vitro studies indicate that it may undergo oxidative demethylation by CYP3A4. Other CYP3A4 substrates have been associated with an increase in colchicine plasma t½ and the emergence of colchicine toxicity.

Elimination

Colchicine is largely excreted (80 %) in unchanged form and as metabolites in the faeces. Only 10 to 20 % is excreted in the urine, although this increases in patients with liver disease. The plasma t½ of colchicine is ~ 9 hours, but colchicine can be detected in leucocytes and in the urine for at least 9 days after a single intravenous dose.

<u>Special populations</u>

Renal impairment

Colchicine is significantly excreted in urine in healthy subjects. Clearance of colchicine is

decreased in patients with impaired renal function. Total body clearance of colchicine was reduced by 75 % in patients with end-stage renal disease undergoing dialysis.

Paediatric population

No pharmacokinetics data are available in children.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Isopropyl alcohol

Lactose monohydrate

Povidone

Pregelatinised starch

Purified water

Stearic acid

Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Pack sizes of 30 or 50 tablets are packed in white opaque round HDPE container with child resistant cap containing polyester fiber and a silica gel canister inside.

COLCHICINE 0,5 mg ACTIVO tablets can also be packed in a white opaque Alu/Alu foil base film with a plain 25 µ Aluminium Foil with 6-8 gsm HSL lidding foil blister strips. The blister strip is packed in an outer carton.

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

Activo Health (Pty) Ltd

Block B, Arena Office Park

272 West Avenue

Centurion

0157

8. REGISTRATION NUMBER(S)

50/3.3/0836

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 August 2022

10. DATE OF REVISION OF THE TEXT