1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

ASPEN COLCHICINE tablet

2 QUALITATIVE AND QUANTITATIVE

Each tablet of ASPEN COLCHICINE contains 0,5 mg of colchicine.

Contains sugar: Lactose monohydrate 64,8 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, round, biconvex tablet bisected on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ASPEN COLCHICINE is indicated for 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) by mouth immediately, followed by 0,5 mg (1 tablet) every 2 hours until pain relief is obtained or gastrointestinal symptoms like 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 ASPEN COLCHICINE to avoid cumulative toxicity.

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

Elderly

ASPEN COLCHICINE should be given with caution to the elderly (see section 4.3).

Paediatric population

There are no data available.

Method of administration

For oral use.

4.3 Contraindications

ASPEN COLCHICINE is contraindicated in:

- Patients with hypersensitivity to colchicine or to any of the excipients in ASPEN COLCHICINE (see section 6.1).
- Pregnancy and lactation (see section 4.6).
- Patients with blood dyscrasias: myelosuppression, leukopenia, granulocytopenia, thrombocytopenia and aplastic anaemia.
- Women of childbearing potential unless they are using effective contraceptive measures.
- Patients with severe renal impairment (creatinine clearance < 30 mL/min) (see section 4.2).

- 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 ASPEN COLCHICINE in therapeutic doses (see section 4.8).
- Combination with macrolide antibiotics and pristinamycin.

4.4 Special warnings and precautions for use

Fatal overdoses

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 ASPEN COLCHICINE should be withdrawn or the dose reduced if adverse gastrointestinal effects occur.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

Elderly population

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

Excipients

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take ASPEN COLCHICINE.

4.5 Interaction with other medicines and other forms of interaction

ASPEN COLCHICINE 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 ASPEN 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 (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 ASPEN COLCHICINE 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 ASPEN COLCHICINE 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 ASPEN COLCHICINE can increase the undesirable effects of colchicine with potentially fatal consequences (see section 4.3)

Oral anticoagulants: Concomitant administration of ASPEN COLCHICINE 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 ASPEN COLCHICINE and for 8 days after its cessation may be required.

Thiazide diuretics: May increase serum uric levels and interfere with the activity of ASPEN COLCHICINE.

Cimetidine and tolbutamide: Reduce metabolism of colchicine and thus plasma levels of ASPEN COLCHICINE increase.

Grapefruit juice: May increase plasma levels of ASPEN COLCHICINE as grapefruit juice is a moderate inhibitor of CYP3A4. Grapefruit juice should therefore not be taken together with ASPEN COLCHICINE.

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 ASPEN 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.

Alcohol

Concomitant use of ASPEN COLCHICINE 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 ASPEN COLCHICINE 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

Use of ASPEN COLCHICINE is contraindicated during pregnancy (see section 4.3).

Pregnancy

ASPEN COLCHICINE is genotoxic *in vitro* and *in vivo*, and is teratogenic in animal studies and there are suggestions of a risk of foetal chromosome damage. ASPEN COLCHICINE is therefore contraindicated in pregnancy (see section 4.3). Women of childbearing potential have to use effective contraception during treatment.

Breastfeeding

Colchicine, as contained in ASPEN COLCHICINE is excreted in breast milk. Therefore, use of ASPEN COLCHICINE is contraindicated in women who are breastfeeding (see section 4.3).

Fertility

Colchicine administration in animals induces significant reductions in fertility.

Women of childbearing potential

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

4.7 Effects on ability to drive and use machines

ASPEN COLCHICINE 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 ASPEN COLCHICINE do not adversely affect their ability to do so safely (see section 4.8).

4.8 Undesirable effects

a) Summary of safety profile

ASPEN COLCHICINE frequently causes nausea, vomiting, abdominal pain and diarrhoea.

b) Tabulated list of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Blood and the lymphatic system disorders			Bone marrow suppression with, agranulocytosis, thrombocytopenia, aplastic anaemia, leukopenia, neutropenia*
Nervous system disorders			Peripheral neuritis, peripheral neuropathy
Respiratory, thoracic and mediastinal disorders			
Vascular disorders			Hypotension (with large doses)
Gastrointestinal disorders	Nausea, vomiting, abdominal pain and diarrhoea.**	Burning of the throat	Profuse diarrhoea, gastrointestinal haemorrhage

Hepatobiliary disorders			Hepatotoxicity, hepatic damage
Skin and subcutaneous tissue disorders		Urticaria, morbilliform eruptions	Burning of the skin, skin rashes, alopecia
Musculoskeletal and connective tissue disorders			Myopathy, rhabdomyolysis
Renal and urinary disorders			Renal damage, dehydration
Reproductive system and breast disorders			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.

** ASPEN COLCHICINE 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: https://www.sahpra.org.za/health-products-vigilance/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9 Overdose

Symptoms

Colchicine, as contained in ASPEN 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).

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 0,1mg/kg bodyweight within 1 hour of presentation and children who have ingested any amount of ASPEN COLCHICINE 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 ASPEN COLCHICINE 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

Category and Class: A 3.3 Anti-gout preparations

Pharmacotherapeutic group: Preparations with no effect on uric acid metabolism

ATC code: M04AC01

Mechanism of action

Colchicine is an anti-inflammatory medicine 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 rapidly, but variable absorbed after oral administration. Peak plasma concentrations are seen between 0,5 to 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 seen in the kidney, liver, and spleen, but it apparently 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 approximately 9 hours. Other CYP3A4 substrates have been associated with an increase in colchicine plasma $t_{1/2}$ and the emergence of colchicine toxicity.

Elimination

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin, lactose monohydrate, magnesium stearate, purified talc, starch maize

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister pack: 24 months

Polypropylene container: 48 months

6.4 Special precautions for storage

Store at or below 25 °C, in airtight containers.

Protect from light.

Keep in original packaging until required for use.

6.5 Nature and contents of container

12 tablets are packed in a white polypropylene container and sealed with a white low density polyethylene snap-on cap together with a white foam insert or rayon coil. The container is packed with a leaflet.

12 tablets are packed in a PVC blister with aluminium foil backing. There are 6 tablets per blister strip and two blisters strips are packed together with a leaflet into a unit carton.

Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8 REGISTRATION NUMBER

C0822 (Act 101/1965)

9 DATE OF FIRST AUTHORISATION

Date of registration: Old Medicine

10 DATE OF REVISION OF TEXT

29 July 2021

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

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