1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S2

PROPRIETARY NAME AND DOSAGE FORM

ASPEN COLCHICINE DS (tablet)

COMPOSITION

Each tablet of ASPEN COLCHICINE DS contains 1,0 mg of colchicine.

Excipients:

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

Contains sugar: Lactose monohydrate 129,60 mg

CATEGORY AND CLASS

A 3.3 Antigout preparations

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Colchicine is an anti-inflammatory agent. Colchicine diminishes lactic acid production by leucocytes directly and diminishes phagocytosis.

Pharmacokinetic properties

The absorption of oral colchicine is rapid but variable. Peak plasma concentrations occur 0,5 to 2 hours after dosing. 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 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 $t_{½}$ and the emergence of colchicine toxicity.

Only 10 to 20 % is excreted in the urine, although this increases in patients with liver disease. The kidney, liver and spleen also contain high concentrations of colchicine, but it apparently is largely excluded from heart, skeletal muscle and brain. The plasma $t_{½}$ 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.

INDICATIONS

ASPEN COLCHICINE DS is indicated for emergency treatment of acute attacks of gout.

CONTRAINDICATIONS

ASPEN COLCHICINE DS is contraindicated:

- If hypersensitivity to colchicine or any components of ASPEN COLCHICINE DS has been experienced (see COMPOSITION).
- In patients undergoing haemodialysis since ASPEN COLCHICINE DS cannot be removed by dialysis or exchange transfusion.
- In patients with severe renal impairment (creatinine clearance less than 10 ml/minute) (see DOSAGE AND DIRECTIONS FOR USE).
- Patients with renal or hepatic impairment should not be given ASPEN COLCHICINE DS in conjunction with P-gp (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 with ASPEN COLCHICINE DS in therapeutic doses (see INTERACTIONS and WARNINGS AND SPECIAL PRECAUTIONS).

- In patients with blood disorders: myelosupression, leucopenia, granulocytopenia, thrombocytopenia and aplastic anaemia.
- During pregnancy (see HUMAN REPRODUCTION).

WARNINGS AND SPECIAL PRECAUTIONS

Fatal overdoses

Fatal overdoses have been reported with ASPEN COLCHICINE DS in adults and children. Keep ASPEN COLCHICINE DS away from children. ASPEN COLCHICINE DS 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 ASPEN COLCHICINE DS (see CONTRAINDICATIONS).

Blood dyscrasias

Myelosupression, leucopenia, granulocytopenia, thrombocytopenia and aplastic anaemia have been reported (see CONTRAINDICATIONS).

P-gp and/or CYP3A4 inhibitor interactions

Coadministration of ASPEN COLCHICINE DS with strong CYP3A4 inhibitors has resulted in life-threatening interactions and death (see CONTRAINDICATIONS and INTERACTIONS).

Neuromuscular toxicity

Myotoxicity including rhabdomyolysis may occur, especially in combination with other medicines known to cause this effect. Concomitant administration of ASPEN COLCHICINE DS with medicines such as ciclosporin and HMG-CoA reductase inhibitors

(e.g. simvastatin) may increase the undesirable effects of ASPEN COLCHICINE DS. Clinical and biological monitoring (measurement of creatinine kinase) is required. Do not exceed several days of treatment with ASPEN COLCHICINE DS (see INTERACTIONS).

Effects on ability to drive and use machines

ASPEN COLCHICINE DS is not expected to adversely affect the ability to drive or operate machinery safely (see SIDE EFFECTS). The patient should however determine how ASPEN COLCHICINE DS 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.

Excipients

ASPEN COLCHICINE 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, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take ASPEN COLCHICINE DS.

INTERACTIONS

P-glycoprotein (P-gp) or strong CYP3A4 inhibitors: ASPEN COLCHICINE DS is a substrate for P-glycoprotein and the cytochrome P450 isoenzyme CYP3A4. Inhibitors of these may increase ASPEN COLCHCINE DS blood concentrations and the potential for toxicity. Life-threatening or fatal interactions have been reported when ASPEN COLCHICINE DS was given with clarithromycin, erythromycin, telithromycin, ciclosporin, ritonavir, atazanavir, indinavir, itraconazole, ketoconazole or calcium channel antagonists such as verapamil and diltiazem. 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

ASPEN COLCHICINE DS dose may need to be adjusted. Such combinations should be avoided in patients with renal or hepatic impairment (see CONTRAINDICATIONS).

Cases of myopathy and rhabdomyolysis have been reported in patients taking ASPEN COLCHICINE DS with statins, fibrates, ciclosporin, or digoxin.

Alcohol: Concomitant use of ASPEN COLCHICINE DS 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 ASPEN COLCHICINE DS 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 ASPEN COLCHICINE DS 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 co-trimoxazole, 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.

Bone marrow depressants or radiation therapy: Additive bone marrow depression may occur and dosage reduction of ASPEN COLCHICINE DS may be required.

Vitamin B_{12}: Absorption of this vitamin may be impaired by chronic administration of ASPEN COLCHICINE DS; higher levels of the vitamin may be required.

HMG-CoA reductase inhibitors: Cases of myopathy, including rhabdomyolysis, have been reported with statins and co-administration with ASPEN COLCHICINE DS and caution should be exercised. Patients should be advised to report muscle pain or weakness.

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

HUMAN REPRODUCTION

ASPEN COLCHICINE DS is contraindicated in pregnancy.

Pregnancy

ASPEN COLCHICINE DS is known to be teratogenic in animals and there are suggestions of a risk of foetal chromosome damage.

Lactation

ASPEN COLCHICINE DS is distributed into breast milk. ASPEN COLCHICINE DS may be used with caution during breastfeeding.

DOSAGE AND DIRECTIONS FOR USE

Acute attacks of gout in adult patients:

Take 1 mg (one tablet) immediately, followed by 0,5 mg (half a tablet) 2 hourly until pain is

relieved or until vomiting or diarrhoea occur.

A maximum dosage of 6 mg (six tablets) must not be exceeded.

A minimum of 3 days, but preferably 7 days, should elapse between courses of gout treatment with ASPEN COLCHICINE DS to avoid cumulative toxicity.

Creatinine clearance:

GFR 10 to 50 ml/minute, 50 % of normal dose.

GFR less than 10 ml/minute, treatment with ASPEN COLCHICINE DS must be avoided (see CONTRAINDICATIONS).

Elderly:

ASPEN COLCHICINE DS should be given with caution to the elderly (see WARNINGS AND SPECIAL PRECAUTIONS).

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

SIDE EFFECTS

Blood and the lymphatic system disorders

Less frequent: Bone marrow depression with agranulocytosis, thrombocytopenia, aplastic anaemia, leucopenia, neutropenia

Nervous system disorders

Less frequent: Peripheral neuritis

Vascular disorders

Frequency unknown: Hypotension (large doses)

Gastrointestinal disorders

Frequent: Nausea, vomiting, abdominal pain and diarrhoea ASPEN COLCHCINE DS should be withdrawn or the dose reduced if gastrointestinal side effects occur

Less frequent: Burning of the throat, gastrointestinal haemorrhage

Hepato-biliary disorders

Frequency unknown: Hepatic damage

Skin and subcutaneous tissue disorders

Frequent: Alopecia

Less frequent: Burning of the skin and rashes, urticaria, morbilliform eruptions

Musculoskeletal, connective tissue and bone disorders

Less frequent: Myopathy, rhabdomyolysis

Renal and urinary disorders

Frequency unknown: Renal damage and dehydration (large doses)

Reproductive system and breast disorders

Less frequent: Azoospermia, reversible upon cessation of treatment

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

Symptoms

ASPEN COLCHICINE DS 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.

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 features (which occur up to 1 day after ingestion) include nausea, vomiting, abdominal pain and diarrhoea.

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. Features occurring after 1 to 7 days include confusion, decreased cardiac output, cardiac dysrhythmias, renal and hepatic impairment, respiratory distress, hyperpyrexia, and bone marrow depression with leucopenia followed by rebound leucocytosis. 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. Alopecia and rebound leucocytosis can occur. A toxic epidermal necrolysis-like reaction has also been reported. The lethal dose varies.

Treatment

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; children who have ingested any amount of ASPEN COLCHICINE DS 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. Gastric lavage

may be an alternative in adults who present within 1 hour of a potentially life-threatening overdose. Management is mainly symptomatic and supportive, with attention given to respiration pulse, blood pressure 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 as they do not enhance ASPEN COLCHICINE DS elimination (see CONTRAINDICATIONS). Blood and urine concentrations are of no use diagnostically.

IDENTIFICATION

A round, white to off-white flat, bevelled edged tablet, bisected on one side.

PRESENTATION

6 tablets are packed in an opaque white polyvinylchloride film sealed with silver aluminium foil backing or in an opaque white polyvinylchloride, polyvinylidene chloride film sealed with silver aluminium foil or in an opaque white polyvinylchloride, polyethylene, polyvinylidene chloride film sealed with silver aluminium foil backing. The blister strips are packed into an outer cardboard carton together with a leaflet.

Not all packs are necessarily marketed.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Store in airtight containers.

Protect from light.

Keep the blisters in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

41/3.3/0260

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

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