

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Colchicine 500microgram Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 micrograms of colchicine.

Excipient with known effect:

One tablet contains 59 mg lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

A white to off white, round, 6 mm diameter, flat tablet with bevelled edges, debossed with "0.5" on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

- Colchicine is indicated for the treatment of acute gout when NSAIDs are contraindicated or are not tolerated by the patient.
- Colchicine is indicated for the prophylaxis of gout attack during initiation of urate-lowering therapy when NSAIDs are contraindicated or are not tolerated by the patient.

4.2 Posology and method of administration

Posology

Adults

Treatment of acute gout attack:

One 500 microgram tablet two to four (2-4) times daily until symptoms are relieved.

The course of treatment should end when symptoms are relieved or when a total of 6 mg (twelve 500 microgram tablets) have been taken. Treatment should be stopped earlier in the event of gastrointestinal symptoms or no improvement of the condition after 2 to 3 days. No more than 6 mg of colchicine tablets should be taken as a course of treatment.

After completion of a course, another course should not be started for at least three days (72 hours).

If diarrhoea or vomiting occurs, Colchicine Tablets should be discontinued immediately as these may be the first signs of an intoxication.

Prophylaxis of gout attack:

0.5 – 1 mg per day (to be taken in the evening).

Paediatric population

Colchicine should not be used in children and adolescents.

Specific groups

Concomitant treatment of colchicine with several drugs, mostly inhibitors of cytochrome P450 3A4 (CYP3A4)/P-glycoprotein have been shown to increase the risk for colchicine toxicity. If a patient has received concomitant therapy with a moderate or potent CYP3A4 inhibitor or with a P-glycoprotein inhibitor, the maximum recommended dosage of oral colchicine should be reduced and should be carefully monitored for adverse effects of colchicine.

Patients with renal impairment

In patients with mild and moderate renal impairment, the dose is 0.5 mg per day and should be carefully monitored for adverse effects of colchicine.

For patients with severe renal impairment, see section 4.3.

Patients with hepatic impairment

In patients with mild and moderate hepatic impairment, the dose is 0.5 mg per day and should be carefully monitored for adverse effects of colchicine.

For patients with severe hepatic impairment, see section 4.3.

Method of Administration

For oral administration

Tablets should be swallowed whole with a glass of water.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Patients with blood dyscrasias
- Patients with severe renal impairment
- Patients with severe hepatic impairment

4.4 Special warnings and precautions for use

Colchicine is potentially toxic so it is important not to exceed the dose prescribed by a medical specialist 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.

If patients develop signs or symptoms that could indicate a blood cell dyscrasia, such as fever, stomatitis, sore throat or prolonged bleeding, treatment with colchicine should be immediately discontinued and a full haematological investigation should be conducted.

Caution is advised in case of:

- liver or renal impairment
- cardiovascular disease
- gastrointestinal disorders
- elderly and debilitated patients
- patients with abnormalities in blood counts

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 count are essential. If skin abnormalities (petechiae) occur, blood counts should be checked immediately.

Macrolides, CYP3A4 inhibitors, ciclosporin, HIV protease inhibitors, calcium channel blockers, and statins may cause clinically significant interactions with colchicine which may lead to colchicine-induced toxicity (see section 4.5).

Co-administration with P-gp inhibitors and/or strong CYP3A4 inhibitors will increase the exposure to colchicine, which may lead to colchicine-induced toxicity including fatalities. If treatment with a P-gp inhibitor or a strong CYP3A4 inhibitor is required in patients with normal renal and hepatic function, a reduction in colchicine dosage is recommended (see sections 4.2 and 4.5) and patients should be carefully monitored for adverse effects of colchicine.

For patients with an impaired renal or hepatic function, the combined use of colchicine and P-gp inhibitors and/or strong CYP3A4 inhibitors should be avoided whenever possible, as it may be difficult to forecast and control systemic exposure to colchicine. In those exceptional cases where continuation of colchicine when starting P-gp inhibitors and/or strong CYP3A4 inhibitors is considered a benefit, despite the potential risk of overdose, significant dose reductions of colchicine dose and careful clinical monitoring should be applied.

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Long-term use of colchicine may be associated with vitamin B12 deficiency.

In case colchicine is used for treatment of acute gout or for prophylaxis of a gout attack during initiation of urate-lowering therapy

Patients should be carefully informed about the potential risk of a possible pregnancy and about effective contraception measures to be followed. Female patients should use effective contraception during and for at least three months following termination of colchicine therapy (see section 4.6). Based on concerns about a potential damage to sperm cells (see section 5.3), male patients should not father a child during and for at least 6 months following termination of colchicine therapy (see section 4.6).

Paediatric population

No long-term safety data are available in paediatric patients.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with other drugs are not or scarcely documented.

Given the nature of the side effects, caution is advised with concomitant administration of drugs that can affect the blood count or have a negative effect on hepatic and/or renal function. In addition, substances such as cimetidine and tolbutamide may reduce metabolism of colchicine and thus increase plasma levels of colchicine.

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 may increase. Toxicity, including fatal cases, have been reported during concurrent use of inhibitors such as macrolides (clarithromycin and erythromycin), ciclosporin, ketoconazole, itraconazole, voriconazole, HIV protease inhibitors, calcium channel antagonists such as verapamil and diltiazem (see section 4.4).

Grapefruit juice may increase plasma levels of colchicine. Grapefruit juice should therefore not be taken together with colchicine.

If treatment with a P-gp inhibitor (e.g. ciclosporin, verapamil or quinidine) or strong CYP3A4 inhibitor (e.g. ritonavir, atazanavir, indinavir, clarithromycin, telithromycin, itraconazole or ketaconazole) is required in patients with normal renal or hepatic function, adjustment of colchicine dosage may be necessary.

Concurrent use of such inhibitors and colchicine should be avoided in patients with renal or hepatic damage (see section 4.4).

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

The risk of myopathy and rhabdomyolysis is increased by a combination of colchicine with statins, fibrates, ciclosporin or digoxin.

4.6 Fertility, pregnancy and lactation

Fertility

Animal research has shown that administration of colchicine may negatively influence spermatogenesis (see section 5.3). Rare cases of reversible oligospermia and azoospermia in men are known from literature.

In case colchicine is used for treatment of acute gout or for prophylaxis of a gout attack during initiation of urate-lowering therapy

Male patients should not father a child during and for at least 6 months following termination of colchicine therapy (see section 4.4). If, nevertheless, pregnancy occurs during this time period, genetic counselling should be tasked.

Pregnancy

Animal studies denote reproductive toxicity (see section 5.3).

In case colchicine is used for treatment of acute gout or for prophylaxis of a gout attack during initiation of urate-lowering therapy

There is a limited amount of data from the use of colchicine in pregnant women with gout. As a precautionary measure, use of colchicine in this patient population and in women of childbearing potential not using effective contraception, should be avoided and may only be considered if other treatment options, including NSAIDs (see section 4.1) and glucocorticoids, are not applicable. Female patients have to use effective contraception during and for at least three months following termination of colchicine therapy (see section 4.4). If, nevertheless, pregnancy occurs during this time period, genetic counselling should be tasked.

Breast-feeding

Colchicine metabolites are found in breast-fed newborns/infants of treated women. There is insufficient information on the effects of colchicine in newborns/infants. Colchicine should not be used in breast-feeding women with gout.

4.7 Effects on ability to drive and use machines

No details are available regarding the influence of colchicine on the ability to drive and use machines. However, the possibility of drowsiness and dizziness should be taken into account.

4.8 Undesirable effects

The following adverse reactions have been observed.

The frequencies are listed under one of the following classifications:

Very common ($\geq 1/10$)

Common ($\geq 1/100$, $< 1/10$)

Uncommon ($\geq 1/1,000$, $< 1/100$)

Rare ($\geq 1/10,000$, $< 1/1,000$)

Very rare ($< 1/10,000$)

Not known (frequency cannot be estimated from the available data)

Blood and lymphatic system disorders

Not known: bone marrow depression with agranulocytosis, aplastic anemia and thrombocytopenia.

Nervous system disorders

Not known: peripheral neuritis, neuropathy.

Gastrointestinal system disorders

Common: abdominal pain, nausea, vomiting and diarrhoea.

Skin and subcutaneous tissue disorders

Not known: alopecia, rash.

Musculoskeletal and connective tissue disorders

Not known: myopathy and rhabdomyolysis.

Reproductive system and breast disorders

Not known: amenorrhoea, dysmenorrhoea, oligospermia, azoospermia.

Respiratory, thoracic and mediastinal disorders

Not known: Pharyngolaryngeal pain

Metabolism and nutrition disorders

Not known: Vitamin B12 deficiency

Paediatric population

No long-term safety data are available in paediatric patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Colchicine has a narrow therapeutic window and is extremely toxic in overdose.

Patients at particular risk of toxicity are those with renal or hepatic impairment, gastro-intestinal or cardiac disease and patients at extremes of age.

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

Clinical:

Symptoms of acute overdosage may be delayed (3 hours on average): nausea, vomiting, abdominal pain, hemorrhagic gastroenteritis, volume depletion, electrolyte abnormalities, leukocytosis, hypotension in severe cases. The second phase with life threatening complications develops 24 to 72 hours after drug administration: multisystem organ dysfunction, acute renal failure, confusion, coma, ascending peripheral motor and sensory neuropathy, myocardial depression, pancytopenia, dysrhythmias, respiratory failure, consumption coagulopathy. 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.

Treatment:

No antidote is available.

Elimination of toxins by gastric lavage within one hour of acute poisoning.

Consider oral activated charcoal in adults who have ingested more than 0.1mg/kg bodyweight within 1 hour of presentation and in children who have ingested any amount within 1 hour of presentation.

Haemodialysis has no efficacy (high apparent distribution volume).

Close clinical and biological monitoring in hospital environment.

Symptomatic and supportive treatment: control of respiration, maintenance of blood pressure and circulation, correction of fluid and electrolytes imbalance.

The lethal dose varies widely (7 - 65 mg single dose) for adults but is generally about 20 mg.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: drugs for gout, with no effect on uric acid metabolism.

ATC code: M04AC01

Mechanism of action

The mechanism of action of colchicine in the treatment of gout is not completely known. Urate crystals are phagocytosed by leukocytes. Hereby inflammatory factors are released. Colchicine inhibits these processes. Other properties of colchicine, such as interaction with microtubules, could also contribute to its action. Onset of actions 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.

Maximum plasma concentrations are met usually after 30 to 120 minutes.

Distribution

Plasma protein binding is approximately 30%. It accumulates in leucocytes.

Elimination

Colchicine is partially metabolized in the liver and then then in part via the bile. It is largely excreted (80%) in unchanged form and as metabolites in the faeces. 10-20% is excreted in the urine. The plasma half-life is 30-60 minutes and approximately 60 hours in leukocytes.

Paediatric population

No pharmacokinetics data are available in children.

5.3 Preclinical safety data

Colchicine causes DNA damage *in vitro* and chromosomal aberrations were observed *in vivo*. No toxicity data are available from own preclinical research.

Studies in animals have shown that colchicine-induced disruption of microtubule formation has an effect on meiosis and mitosis. After colchicine exposure a reduced sperm count and sperm cells with abnormal morphology have been demonstrated in male animals. The doses used in these studies were substantially higher than the dose prescribed for use in patients.

High doses of colchicine can cause teratogenicity and embryo toxicity in mice, rats and rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Pregelatinised starch
Sodium starch glycolate
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

White opaque PVC/ plain push through aluminum foil.

Blisters : 20 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd

(Trading style: Accord)

Whiddon Valley

Barnstaple

Devon

EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PL 0142/0918

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/04/2015

10 DATE OF REVISION OF THE TEXT

29/07/2025