SUMMARY OF PRODUCT CHARACTERISTICS

Important warning!
Because of the narrow therapeutic range of colchicine, the recommended maximum dose must not be exceeded. Overdosing, including by ignoring interactions, can lead to a fatal, very painful and irreversible poisoning with a fatal outcome. Please refer to sections 4.4, 4.5., 4.8 and 4.9 of this SmPC.
The medicinal product must be kept out of reach of others before and after use.

1 NAME OF THE MEDICINAL PRODUCT

Colchicine 500 microgram tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 microgram of Colchicine

Excipients with known effect:
Colchicine 500 microgram tablets contain 50.50 mg lactose monohydrate, equivalent to 47.82 mg of lactose anhydrous as a diluent.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
White to off white, biconvex round uncoated tablets with 'L' debossed on one side and plain on other side. (ca. 5mm diameter, ca. 2.6 mm thickness)

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adult

- 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 a 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

Gout

Acute gout attack
2 to 3 times daily 0.5 mg, possibly preceded by an initial dose of 1 mg. Treatment should end until the acute attack resolves, or earlier in the event of gastrointestinal symptoms and no improvement after 2 to 3 days.

No more than 6 mg should be taken as a course of treatment. After completion of a course, another course should not be started for at least 3 days (72 hours).

If diarrhoea or vomiting occurs, Colchicine 500 microgram 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 500 microgram Tablets 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 severe renal impairment see section 4.3 contraindications

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 severe hepatic impairment see section 4.3 contraindications.

Method of Administration
Oral route.
Tablet should be swallowed 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 disease
- 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 or 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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

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

Where 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).

A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with a P-gp inhibitor or moderate or strong CYP3A4 inhibitor is required (see section 4.4). A 4-fold reduction in colchicine dosage is recommended when co-administered with a P-gp inhibitor and/or a strong CYP3A4 inhibitor. A 2-fold reduction in colchicine dosage is recommended when co-administered with a moderate CYP3A4 inhibitor

Reversible malabsorption of cyanocobalamine (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.

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 offered.

Pregnancy

Animal studies denote reproductive toxicity (see section 5.3).

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 must 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 offered.

Breast-feeding

Colchicine/metabolites is /are found in breastfed 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 data 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 unknown, unless listed under one of the following classifications:
Very common (≥ 1/10)
Common (≥ 1/100, < 1/10)
Uncommon (≥ 1/1,000, < 1/100)
Rare (≥ 1/10,000, < 1/1,000)
Very rare (< 1/10,000)

Blood and lymphatic system disorders
Bone marrow depression with agranulocytosis and aplastic anaemia.

Nervous system disorders
Peripheral neuritis, neuropathy

Gastrointestinal disorders
Common: abdominal pain, nausea, vomiting and diarrhoea

Hepatobiliary disorders
Not known: hepatotoxicity

Renal and urinary disorders
Not known: renal damage.

Skin and subcutaneous tissue disorders
Alopecia, rash

Musculoskeletal and connective tissue disorders
Myopathy and rhabdomyolysis

Reproductive system and breast disorders
Amenorrhoea, dysmenorrhoea, oligospermia, azoospermia

Respiratory, thoracic en mediastinal disorders
Pharyngolaryngeal pain

Metabolism and nutrition disorders
Vitamin B12 deficiency

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

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, haemorrhagic gastroenteritis, volume depletion, electrolyte abnormalities, leucocytosis, 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 leucocytosis 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 activate charcoals in adults who have ingested more than 0.1 mg/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 strongly (7 – 65 mg in one dose), but for adults it 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**.**

In the AGREE (Acute Gout Flare Receiving Colchicine Evaluation) study low- and high-dose colchicine were compared using a randomized, placebo-controlled design. The high-dose prolonged colchicine regimen (4.8 mg total over 6 hours) was compared with a placebo and a low-dose abbreviated regimen (1.8 mg total over 1 hour, i.e. 1.2 mg followed by 0.6 mg in 1 hour). Both colchicine regimens were significantly more effective than placebo, with 32.7% responders in the high-dose group, 37.8% responders in the low-dose group, and 15.5% responders in the placebo group ($P = 0.034$ and $P = 0.005$, respectively, versus placebo). The results at the primary 24-hour end point demonstrate superior safety of low-dose colchicine, without loss of efficacy, relative to high-dose colchicine for early acute gout flare (self-administered within 12 hours of flare onset). The pharmacokinetic analysis performed in this study showed that the colchicine plasma concentration was decreased substantially from about 12 hours after administration in healthy volunteers.

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 of colchicine 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 urine. The plasma half-life is 30-60 minutes and approximately 60 hours in leukocytes.

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.

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 op 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
Pregelatinised starch (maize)
Sodium starch glycolate
Colloidal anhydrous silica
Stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister Pack - 48 months
Bottle Pack – 36 months
Shelf life after opening the bottle is 100 days

6.4 Special precautions for storage

Store in the original container protected from light**.**

6.5 Nature and contents of container

Blister of PVC/PVDC with Aluminium lidding foil. Each pack contains 10, 14, 20, 28, 30, 40, 56, 60, 84, 90, 98 and 100 tablets.

HDPE bottle with child-resistant white polypropylene closure. Each bottle contains 30 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Ria Generics Limited,
36 Ingleby Way,
Wallington, Surrey SM6 9LR,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 36282/0015

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/10/2018

10 DATE OF REVISION OF THE TEXT

05/02/2021