Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Colchicine 500 microgram Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 micrograms colchicine

Excipient(s) with known effect:
Each tablet contains 50.85 mg lactose monohydrate equivalent to 48.31 mg lactose (see section 4.4).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
5.5 mm, round shallow biconvex white tablet, plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults
Treatment of acute gout.
Prophylaxis of gout attack during initiation of therapy with allopurinol and uricosuric drugs

Paediatric population
Colchicine is indicated in Familial Mediterranean Fever for prophylaxis of attacks and prevention of amyloidosis.

4.2 Posology and method of administration

Posology

Adults
Treatment for acute gout attack:

1 mg (2 tablets) to start followed by 500 micrograms (1 tablet) after 1 hour. No further tablets should be taken for 12 hours.

After 12 hours, treatment can resume if necessary with a maximum dose of 500 micrograms (1 tablet) every 8 hours until symptoms are relieved.

The course of treatment should end when symptoms are relieved or when a total of 6 mg (12 tablets) has been taken. No more than 6 mg (12 tablets) 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).

Prophylaxis of gout attack during initiation of therapy with allopurinol and uricosuric drugs:

500 micrograms twice daily.

The treatment duration should be decided after factors such as flare frequency, gout duration and the presence and size of tophi have been assessed.

Patients with renal impairment
Use with caution in patients with mild renal impairment. For patients with moderate renal impairment, reduce dose or increase interval between doses. Such patients should be carefully monitored for adverse effects of colchicine (see also section 5.2).

For patients with severe renal impairment, see section 4.3.

Patients with hepatic impairment
Use with caution in patients with mild/moderate hepatic impairment. Such patients should be carefully monitored for adverse effects of colchicine.

For patients with severe hepatic impairment, see section 4.3.

Elderly

Use with caution.

Paediatric population
Familial Mediterranean fever:

For paediatric use, colchicine should only be prescribed under the supervision of a medical specialist with the necessary knowledge and experience.

A starting dose should be administered orally based on age:
• 0.5mg/day in children less than 5 years of age
• 1mg/day in children from 5 to 10 years of age
• 1.5mg/ day in children over 10 years,

The dose could be given as a single dose or doses higher than 1mg/day could be divided and given twice daily.

In children with amyloid nephropathy, higher daily doses up to 2 mg/day might be needed.

Careful monitoring is needed in the presence of impaired renal or liver function. For these patients, the starting dose should be reduced by 50% (e.g. ≤ 1 mg/day).

When 0.25mg doses are required, e.g. to control disease in patients who do not clinically respond to the standard dosage, use of this 0.5 mg tablet is not appropriate.

Method of administration
For oral administration

Tablets should be swallowed whole with a glass of water. For patients who have difficulty in swallowing (including small children), the tablet can be dissolved in a glass of water which should be taken immediately.

4.3 Contraindications

· Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
· Patients with blood dyscrasias
· Pregnancy
· Breastfeeding
· Women of childbearing potential unless using effective contraceptive measures
· Patients with severe renal impairment
· Patients with severe hepatic impairment
· Colchicine should not be used in patients undergoing haemodialysis since it cannot be removed by dialysis or exchange transfusion.

· Colchicine is contraindicated in patients with renal or hepatic impairment who are taking a P-glycoprotein (P-gp) inhibitor or a strong CYP3A4 inhibitor (see section 4.5).

4.4 Special warnings and precautions for use

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

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.

Caution is advised in case of:
· liver or renal impairment
· cardiovascular disease
· gastrointestinal disorders
· elderly and debilitated patients
· patients with abnormalities in blood counts

Patients with liver or renal impairment should be carefully monitored for adverse effects of colchicine (see section 5.2).

Co-administration with P-gp inhibitors and/or moderate 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 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).

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

4.5 Interaction with other medicinal products and other forms of interactions

Colchicine is a substrate for both CYP3A4 and the transport proteinP-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 and erythromycin), ciclosporin, ketoconazole, itraconazole, voriconazole, HIV protease inhibitors, calcium channel blockers (verapamil and diltiazem) and disulfiram (see section 4.4).

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 ketaconazole) (see section 4.3).

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.

The magnitude of interactions with strong and moderate CYP3A4 inhibitors as well as with P-gp inhibitors from performed *in vivo* studies is summarised in the table below:

Single dose of 0.6 mg colchicine without or with:	**Number of subjects**	**% change in colchicine pharmacokinetic parameters**		**Guidance for dose reduction:**
		C_{max}	**AUC_{o-t}**	
Strong CYP3A4 inhibitors Clarithromycin 250 mg twice daily for 7 days	N=23	297	339	4-fold Acute gout regimen to be repeated no earlier than 3 days.
Ketoconazole 200 mg twice daily for 5 days	N=24	190	287	
Ritonavir 100 mg twice daily for 5 days	N=18	267	345	
Moderate CYP3A4 inhibitors Verapamil ER 240 mg once daily for 5 days	N=24	130	188	2-fold Acute gout regimen to be repeated no earlier than 3 days.
Diltiazem ER 240 mg once daily for 7 days	N=20	129	177	
Grapefruit juice 240 ml twice daily for 4 days	N=21	93	95	
Potent P-gp inhibitors Cyclosporin 100 mg single dose	N=23	324	317	4-fold Acute gout regimen to be repeated no earlier than 3 days.

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 reduce metabolism of colchicine and thus plasma levels of colchicine increase.

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

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.

Concomitant administration of colchicine, a P-glycoprotein substrate, with macrolide antibiotics, such as azithromycin, has been reported to result in increased serum levels of the P-glycoprotein substrate, in this case colchicine. Clinical monitoring, and possibly serum levels of colchicine, during treatment with azithromycin and after its discontinuation are necessary.

4.6 Fertility, pregnancy and lactation

Fertility
Colchicine administration in animals induces significant reductions in fertility.

Pregnancy
Colchicine is genotoxic in vitro and in vivo, and is teratogenic in animal studies (see section 5.3). Colchicine is therefore contraindicated in pregnancy (see section 4.3).

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

Breastfeeding
Colchicine is excreted in breast milk. Therefore, use of colchicine is contraindicated in women who are breastfeeding (see section 4.3).

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 > 1/10
Common > 1/100 and < 1/10
Uncommon > 1/1000 and < 1/100
Rare > 1/10 000 and < 1/1000
Very rare < 1/10 000
Not known (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.
Not known: gastrointestinal haemorrhage.

Hepatobiliary disorders
Not known: hepatotoxicity

Skin and subcutaneous tissue disorders
Not known: alopecia, rash.

Musculoskeletal and connective tissue disorders
Not known: myopathy and rhabdomyolysis.

Renal and urinary disorders
Not known: renal damage.

Reproductive system and breast disorders
Not known: amenorrhoea, dysmenorrhoea, oligospermia, azoospermia.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971_; Fax: +353 1 6762517_. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

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

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.

Colchicine prophylaxis (0.6 mg twice daily) during initiation of allopurinol for chronic gouty arthritis reduced the frequency and severity of acute flares, and reduced the likelihood of recurrent flares. Treatment may be continued for up to 6 months, based on clinical data. Prospective randomized controlled trials are needed to further evaluate flare prophylaxis for up to 6 months, after 6 months, and over time.

The mechanism of action of colchicine in the treatment of gout is not clearly understood. Colchicine 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

Colchicine is rapidly and almost completely absorbed after oral administration. Maximum plasma concentrations are met usually after 30 to 120 minutes. The terminal half-life is 3 to 10 hours. Plasma protein binding is approximately 30%. Colchicine is partially metabolised in the liver and then in part via the bile. It accumulates in leucocytes. Colchicine is largely excreted (80%) in unchanged form and as metabolites in the faeces. 10-20% is excreted in the urine.

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.
The influence of renal impairment on the pharmacokinetics of colchicine was assessed in a study in patients with familial Mediterranean fever (FMF), 5 women and 4 men, with (n=4) and without (n=5) renal impairment. The mean age was 30 years (range 19-42 years). All 5 patients with renal impairment had biopsy-proven amyloidosis; 4 were on routine hemodialysis and 1 had a serum creatinine CL of 15 ml/min. They could therefore be classified as having severe renal impairment.

Subjects received 1 mg colchicine except for 1 subject with cirrhosis who received 500 micrograms. A 4-fold decrease in colchicine CL was observed in subjects with renal impairment compared to those with normal renal function (0.168 ± 0.063 l/h/kg vs. 0.727 ± 0.110 l/h/kg). The terminal half-life was 18.8 ± 1.2 h for subjects with severe renal impairment and 4.4 ± 1.0 h for those with normal renal function. The volume of distribution was similar between groups. The patient with cirrhosis had a 10-fold lower CL compared to the subjects with normal renal function.

Paediatric population
No pharmacokinetics data are available in children.

5.3 Preclinical safety data

Genotoxicity
In one study, a bacterial test indicated that colchicine has a slight mutagenic effect. However, two other bacterial tests and a test in *Drosophila melanogaster* found that colchicine was not mutagenic.

Tests have shown that colchicine induces chromosomal aberrations and micronuclei, and causes some DNA damage.

Teratogenicity
Tests in animals have shown that colchicine is teratogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Maize Starch
Magnesium Stearate
Starch, pre-gelatinised

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

In-use shelf life:
50 days when stored at or below 25°C.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

High Density Polyethylene (HDPE) containers with polypropylene caps containing 100 or 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Renata Pharmaceuticals (Ireland) Limited
13-18 City Quay
Dublin 2
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22865/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th December 2017
Date of last renewal: 11th November 2022

10 DATE OF REVISION OF THE TEXT

March 2022