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
Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.5 mg (500 micrograms) of colchicine.

Excipients with known effect
Each tablet contains about 80 mg lactose.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White round tablets for oral use.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention and treatment of gout and FMF (familial mediterranean fever).

4.2 Posology and method of administration

Posology

Gout

The patient should be instructed to always have Colchicine at hand, so that therapy can be started at the first sign of an impending attack. Initiation of Colchicine therapy in the later stages of an attack may not completely abate the condition.
The initial dose to relieve an attack is 1 or 2 tablets, followed by 1 tablet each hour or 2 tablets every 2 hours, until the pain is relieved, or nausea, vomiting or diarrhea develops. The total amount of colchicine usually required is variable. A course of therapy may range from 3-6 mg.
A total dose of 6 mg should not be exceeded. The course should not be repeated within three days.

Familial Mediterranean Fever (FMF)

The recommended dosage of colchicine for FMF in adults is 1 mg to 2 mg daily.

Colchicine should be increased as needed to control disease and as tolerated in increments of 0.25 mg/day to maximum recommended daily dose. If intolerable side effects develop, the dose should be decreased in increments of 0.25 mg/day. The total daily colchicine dose may be administered in one to two divided doses.

Renal Impairment:
For mild/moderate renal impairment (creatinine clearance 10-50 ml/minute), reduce dose or increase interval between doses (see also section Contraindications).

Elderly:
To be given with great care.

Children:
FMF: The recommended dosage of colchicine for FMF in pediatric patients 4 years of age and older is based on age. The following daily doses may be given as a single or divided dose twice daily:
Children 4 – 6 years: 0.25 mg to 1.5 mg daily
Children 6 – 12 years: 1 mg to 1.5 mg daily

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

Pregnancy-see section 4.6

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, diarrhea 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 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, 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. The use of colchicine in children is primarily indicated for the indication FMF.

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 renalfunction.

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 inthe 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. It has been reported that co-administration of azithromycin with colchicine leads to increased serum levels of colchicine. During treatment with azithromycin and after discontinuation, clinical follow-up, and potentially follow-up of serum levels of colchicine, is required (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 cyanocobalamine (Vitamin B12) may be inducedby an altered function of the intestinal mucosa.

The risk of myopathy and rhabdomyolysis is increased by a combination ofcolchicine 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 FMF

Since the course of FMF without treatment may also lead to infertility, the use of colchicine should be weighed against the potential risks and may be considered, if clinically needed.

In case colchicine is used for treatment of acute gout or for prophylaxis of agout 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 FMF

A moderate amount of data on pregnant women with FMF indicate no malformative or feto/ neonatal toxicity of colchicine. Since the course of FMF without treatment may also negatively influence pregnancy, the use of colchicine during pregnancy should be weighed against the potential risks andmay be considered, if clinically needed.

In case colchicine is used for treatment of acute gout or for prophylaxis of agout 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 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 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. In lactating mothers with FMF, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Colchicine therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

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 ,aplastic anemia and thrombocytopenia.
Nervous system disorders
Peripheral neuritis, neuropathy, drowsiness, dizziness.
Gastrointestinal disorders
Common: abdominal pain, nausea, vomiting and diarrhea
Hepatobiliary disorders
Hepatotoxicity

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 and mediastinal disorders
Pharyngolaryngeal pain

Metabolism and nutrition disorders
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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

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 bereferred 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 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.

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 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.

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*.

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, corn starch, povidone K25, magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C. Store in the original package Protect from light.

6.5 Nature and contents of container

Blister packs containing 30 tablets.

6.6 Special precautions for disposal

No special requirements.

7 REGISTRATION HOLDER

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