APPROVED PROFESSIONAL INFORMATION FOR KOLCRYS

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

KOLCRYS Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Colchicine 0,5 mg per tablet

Contains sugar: (50,80 mg lactose monohydrate per tablet).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

Round, white to pale yellow coloured tablets, plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

KOLCRYS is indicated for the relief of acute attacks of gout in cases of emergency.

4.2 Posology and method of administration

Posology:

The initial dose is 0,5 mg to 1 mg (1 to 2 tablets) orally immediately, followed by 0,5 mg (1 tablet) every two hours until pain relief is obtained or gastrointestinal symptoms like vomiting or diarrhoea occur. A maximum total treatment course of 6 mg must not be exceeded. The course should not be repeated within three days.

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Renal impairment:

Reduce the dose or increase the interval between doses when given to patients with mild to moderate renal impairment (see section 4.4).

4.3 Contraindications

- Hypersensitivity to colchicine or to any of the inactive ingredients of KOLCRYS (see section 6.1).
- Pregnancy (see section 4.6).
- Patients with hepatic or renal impairment requiring concomitant therapy with CYP3A4 or P-glycoprotein inhibitors (see section 4.5).
- Patients with severe renal impairment (creatinine clearance less than 30 mL/min).
- Patients with severe liver impairment.
- Patients with blood disorders should not use KOLCRYS.
- Patients undergoing haemodialysis, since it cannot be removed by dialysis or exchange transfusion.

4.4 Special warnings and precautions for use

KOLCRYS is potentially toxic, so it is important not to exceed the recommended dose.

KOLCRYS should be given with care to elderly and debilitated patients, as there is a greater risk of cumulative toxicity.

KOLCRYS has a narrow therapeutic window, and should be discontinued if toxic symptoms such as nausea, vomiting, abdominal pain and diarrhoea occur.

KOLCRYS should be used with caution in patients with cardiovascular, mild and moderate hepatic, mild and moderate renal, -or gastrointestinal diseases.

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KOLCRYS is contraindicated in severe renal and hepatic impairment.

A reduction of KOLCRYS dosage or interruption of KOLCRYS treatment is recommended in patients with normal renal and hepatic function, if treatment with a P-glycoprotein or a strong CYP3A4 inhibitor is required (see section 4.5).

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 KOLCRYS should be immediately discontinued and a full haematological investigation should be conducted straight away.

Excipient warning

KOLCRYS contains lactose monohydrate.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take KOLCRYS.

4.5 Interaction with other medicines and other forms of interaction

KOLCRYS is a substrate for P-glycoprotein and the cytochrome P450 isoenzyme CYP3A4. Inhibitors of these may increase blood concentration levels of KOLCRYS and the potential for toxicity.

Life-threatening or fatal medicine interactions have been reported when KOLCRYS was given with the following medicines:

- Macrolides (e.g., erythromycin).
- Calcium channel antagonists (e.g., diltiazem).

KOLCRYS is contraindicated in patients with renal or hepatic impairment who are taking a P-glycoprotein inhibitor (e.g., ciclosporin, verapamil, quinidine) or a strong

CYP3A4 inhibitor (e.g., ritonavir, atazanavir, clarithromycin, telithromycin, itraconazole, ketoconazole) (see section 4.3).

If treatment with a P-glycoprotein inhibitor or a strong CYP3A4 inhibitor is required in patients with normal renal and hepatic function, a reduction in the KOLCRYS dose or an interruption of KOLCRYS treatment is recommended (see section 4.4).

Myopathy and rhabdomyolysis have been reported when taking KOLCRYS with statins, fibrates, ciclosporin and digoxin.

Hydrochlorothiazide may increase serum uric acid and interfere with activity of KOLCRYS.

Caution is advised with concomitant administration of medicine that can affect the blood count or have a negative effect on hepatic and/or renal function, due to the nature of side effects.

Substances such as cimetidine and tolbutamide reduce metabolism of KOLCRYS and thus plasma levels of KOLCRYS increase.

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

KOLCRYS may impair the absorption of vitamin B_{12}.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Colchicine, as in KOLCRYS, is genotoxic *in vivo* and *in vitro* and is teratogenic in animals.

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The use of KOLCRYS is contraindicated in pregnancy (see section 4.3).

Lactation:

KOLCRYS is distributed into breast milk. KOLCRYS may be used with caution during breastfeeding.

4.7 Effects on ability to drive and use machines:

KOLCRYS is not known to affect the ability to drive a vehicle and use machines. Caution is advised before performing tasks requiring attention until the effects of KOLCRYS are known.

4.8 Undesirable effects

System Organ Class	Frequency	Side effects
Blood and the lymphatic system disorders	Frequency unknown	Bone marrow depression with agranulocytosis, aplastic anaemia, thrombocytopenia
Nervous system disorders	Frequency unknown	Peripheral neuritis, neuropathy
Respiratory disorders	Frequency unknown	Burning of the throat
Gastrointestinal disorders	Frequent Frequency unknown	Abdominal pain, nausea, vomiting, diarrhoea Gastrointestinal haemorrhage
Hepato-biliary disorders	Frequency unknown	Hepatotoxicity
Skin and subcutaneous	Frequency unknown	Alopecia, rash, burning sensation of the skin

tissue disorders		
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Myopathy, rhabdomyolysis
Renal and urinary disorders	Frequency unknown	Renal damage
Reproductive system and breast disorders	Frequency unknown	Amenorrhoea, dysmenorrhoea, oligospermia, azoospermia

Reporting of suspected adverse reactions:

Reporting of suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

KOLCRYS has a narrow therapeutic window and is extremely toxic in overdose. Patients with renal or hepatic impairment, gastrointestinal or cardiac disease and elderly patients are at particular risk of toxicity. Overdose with KOLCRYS is complex and specialist advice should be promptly obtained. Symptoms of overdose may not appear for at least 6 hours. All patients, even in the absence of early symptoms, should be referred for immediate medical assessment.

Symptoms:

The first symptoms of toxicity are a feeling of burning and rawness in the mouth and throat, and difficulty in swallowing This is followed by nausea, vomiting, and diarrhoea. The diarrhoea may be severe and haemorrhagic, and can lead to metabolic acidosis, dehydration, hypotension and 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. Bone marrow depression with leukopenia may be followed by rebound leukocytosis. Multiple organ failure may occur and may manifest as central nervous system (CNS) toxicity, bone marrow depression, hepatocellular damage, muscle damage, respiratory distress, myocardial injury and renal damage.

The patient may develop convulsions, delirium, neuropathy and ascending paralysis of the central nervous system. Death may be due to respiratory distress, cardiovascular collapse, bone marrow depression or sepsis. Alopecia, rebound leukocytosis and stomatitis may occur about 10 days after the acute overdose, in surviving patients.

Treatment:

When treating KOLCRYS overdose or acute poisoning, patients should be carefully monitored for some time to take account of the delayed onset of symptoms. Multiple doses of activated charcoal should be given. Treatment is primarily symptomatic and supportive. Patients may require respiratory assistance, maintenance of blood pressure and circulation and correction of fluid and electrolyte imbalance.
Haemodialysis has no efficacy (high apparent distribution volume).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

A 3.3 Antigout preparations

Pharmacotherapeutic group: Preparations with no effect on uric acid metabolism

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ATC code: M04AC01

Mechanism of action

The anti-inflammatory effect of colchicine in acute gout is selective for this disorder. An acute gout attack may occur as a result of an inflammatory reaction to crystals of monosodium urate that are deposited in the joint tissue from hyperuric body fluids. The inflammatory response involves local infiltration of granulocytes that phagocytise the urate crystals. In synovial tissues and in leukocytes associated with the inflammatory process, lactic acid production is high and this favours a local decrease in pH that fosters further uric acid deposition. Colchicine diminishes lactic acid production by leukocytes directly and by diminishing phagocytosis and thereby interrupts the cycle of urate crystal deposition and inflammatory response that sustains the acute attack.

5.2. Pharmacokinetic properties

Absorption

Colchicine is absorbed rapidly after oral administration. Peak plasma concentrations occur 0,5 – 2 hours after a dose.

Distribution

In plasma, 50 % of colchicine is protein bound.

Metabolism

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, such as cimetidine, have been associated with an increase in colchicine plasma $t_{1/2}$ and the emergence of colchicine toxicity.

Excretion

Most of the medicine is excreted in the faeces however, in normal individuals 10 – 20 % of colchicine is excreted in urine.

Special populations

Renal impairment

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.

Hepatic impairment

In patients with liver disease the hepatic uptake and elimination are reduced and more colchicine is excreted in the urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Povidone

Pregelatinised starch

Stearic Acid

Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C.

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Protect from light and moisture.

Do not remove blister strips from outer carton until required for use.

6.5 Nature and contents of container

Silver Alu/Alu blister strips with 6 tablets per blister strip, provided

in outer cartons of 1 x 6 or 2 x 6, therefore a pack of either 6 or 12 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Forrester Pharma (Pty) Ltd

2 Waterford Mews

Waterford place

Century City

7441

Cape Town

South Africa

8. REGISTRATION NUMBERS

50/3.3/0484

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 12 November 2019

10. DATE OF REVISION OF THE TEXT

29 March 2023