1.3.1.1 Professional Information for Medicines for Human Use

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

CHOLDIX 0.5 mg (tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CHOLDIX 0.5 mg:

Each tablet contains 0,5 mg colchicine.

Contains sugar: lactose monohydrate 49,00 mg.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Off-white to light yellow coloured, round shaped, biconvex uncoated tablet debossed with 'C' on one side and "0.5" on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

CHOLDIX 0.5 mg is indicated for the relief of acute attacks of gout in case of emergency.

4.2. Posology and method of administration

Posology

In acute gout, the initial dose is 0,5 to 1 mg (1 to 2 tablets) by mouth immediately, followed by 0,5 mg (1 tablet) every 2 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 treatment course should not be repeated within 3 days.

Paediatric population:

The safety and efficacy of **CHOLDIX 0.5 mg** in children under the age of 18 years has not been established

Method of administration

Tablets are taken by mouth.

4.3. Contraindications

CHOLDIX 0.5 mg is contraindicated in

- Hypersensitivity to colchicine or to any of the excipients listed in section 6.1.
- Pregnancy
- Patients with blood dyscrasia
- In patients undergoing haemodialysis since colchicine cannot be removed by dialysis or exchange transfusion.
- Patients with renal or hepatic impairment should not be given colchicine in conjunction with P-gp (e.g. ciclosporin, verapamil or quinidine) or potent CYP3A4 inhibitors (e.g. ritonavir, atazanavir, indinavir, clarithromycin, telithromycin, itraconazole or ketoconazole). In these patients, life-threatening and fatal colchicine toxicity has been reported in therapeutic doses.
- Women of childbearing potential unless effective contraceptive measures are taken
- Patients with severe renal dysfunction
- Patients with severe hepatic dysfunction

4.4. Special warnings and precautions for use

CHOLDIX 0.5 mg is potentially toxic; therefore, it is important that the dose as prescribed by a medical specialist with the necessary knowledge and experience is not exceeded. Colchicine has a narrow therapeutic range. Administration should be discontinued for toxic symptoms such as nausea, vomiting, abdominal pain, diarrhoea.

If patients develop signs or symptoms that could indicate blood cell dyscrasias, such as fever, stomatitis, sore throat or prolonged bleeding, treatment with **CHOLDIX 0.5 mg** should be discontinued immediately and a full haematological examination should be performed.

Caution is advised in:

• mild or moderate hepatic and renal impairment

• cardiovascular disorders

• gastrointestinal disorders

• elderly and debilitated patients

• patients with blood count abnormalities.

CHOLDIX 0.5 mg can cause severe bone marrow depression (agranulocytosis, aplastic anaemia, and thrombocytopenia). The change in the blood count can occur gradually, but also very suddenly. Aplastic anaemia in particular has a high risk of death. Periodic inspection of the blood count is necessary. When skin abnormalities develop, the blood count must be checked immediately.

Macrolides, CYP3A4 inhibitors, ciclosporin, HIV protease inhibitors, calcium channel antagonists and statins may cause clinically important interactions with **CHOLDIX 0.5 mg** leading to colchicine-induced toxicity (see section 4.5).

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take **CHOLDIX 0.5 mg**.

4.5. Interaction with other medicines and other forms of interaction

Interactions with other medicines are not or hardly documented. Due to the nature of the adverse reactions, caution should be exercised when co-administering medicinal products that may affect the blood count or adversely affect liver and / or kidney function.

In addition, substances such as cimetidine, and tolbutamide can decrease the metabolism of **CHOLDIX 0.5 mg** and thus increase plasma levels of **CHOLDIX 0.5 mg**.

CHOLDIX 0.5 mg is a substrate for both CYP3A4 and the transport protein P-glycoprotein. Inhibitors of CYP3A4 and P-glycoprotein can increase the levels of **CHOLDIX 0.5 mg** in the blood. Toxicity, including fatalities, has been reported during concomitant use of inhibitors such as macrolides (clarithromycin and erythromycin), ciclosporin, ketoconazole, itraconazole, voriconazole, HIV protease inhibitors, calcium channel antagonists such as verapamil and diltiazem and colchicine.

If treatment with a P-glycoprotein inhibitor or a strong CYP3A4 inhibitor is necessary in patients with normal renal and hepatic function, the **CHOLDIX 0.5 mg** dose may need to be adjusted. Concomitant use of these inhibitors with **CHOLDIX 0.5 mg** should be avoided in patients with kidney or liver damage (see section 4.4).

Grapefruit juice can increase the plasma level of **CHOLDIX 0.5 mg**. Grapefruit juice should therefore not be taken with **CHOLDIX 0.5 mg**.

Reversible malabsorption of cyanocobalamin (vitamin B_{12}) can be induced by altered functioning of the intestinal mucosa.

The risk of myopathy and rhabdomyolysis is increased when **CHOLDIX 0.5 mg** is combined with statins, fibrates, ciclosporin or digoxin.

4.6. Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and female

Animal studies have shown that **CHOLDIX 0.5 mg** is teratogenic. Women of childbearing potential should not take **CHOLDIX 0.5 mg** unless effective contraceptive measures are taken.

Pregnancy

CHOLDIX 0.5 mg is contraindicated in pregnancy.

Breastfeeding

CHOLDIX 0.5 mg is widely excreted in breast milk. Therefore, **CHOLDIX 0.5 mg** should not be used during breastfeeding.

4.7. Effects on ability to drive and use machines

No information is available on the influence of **CHOLDIX 0.5 mg** on the ability to drive and use machines. However, the possibility of drowsiness and dizziness should be taken into account.

4.8. Undesirable effects

a. *Summary of the safety profile*

The most common side-effects are nausea, vomiting, abdominal pain and diarrhoea. **CHOLDIX 0.5 mg** should be withdrawn or the dose reduced if adverse gastrointestinal effects occur. Burning of the skin and throat may also occur. Larger doses may cause profuse diarrhoea, gastrointestinal haemorrhage, skin rashes and renal damage.

b. *Tabulated list of adverse reactions*

The following side effects have been observed. The frequency is unknown, unless stated according to the classification below:

System Organ Class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Unknown	Bone marrow depression with agranulocytosis and aplastic anaemia

Nervous system disorders	Unknown	Peripheral neuritis, neuropathy
Gastrointestinal disorders	Frequent	Abdominal pain, nausea, vomiting and diarrhoea
Skin and subcutaneous tissue disorders	Unknown	Alopecia, rash (rashes)
Musculoskeletal and connective tissue disorders	Unknown	Myopathy and rhabdomyolysis
Reproductive system and breast disorders	Unknown	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 to SAHPRA via the '6.04 Adverse Drug Reactions Reporting Form'. Found under SAHPRA's publications: https://www/sahpra.org.za/Publications/Index/8

4.9. Overdose

Symptoms

Symptoms of overdosage do not appear for at least several hours. The first symptoms are a feeling of burning and rawness in the mouth and throat and difficulty 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 also occur.

Extensive vascular damage and acute renal toxicity with oliguria and haematuria have been reported. Bone marrow depression with leucopenia may be followed by rebound leucocytosis. Multiple organ failure may occur and may manifest as CNS toxicity, bone marrow depression, hepatocellular damage, muscle damage, respiratory distress, myocardial injury and renal damage.

The patient may develop convulsions, delirium, muscle weakness, neuropathy and ascending paralysis of the nervous system.

Death may be due to respiratory depression, cardiovascular collapse, bone marrow depression or sepsis. In surviving patients, alopecia, rebound leucocytosis and stomatitis may occur about 10 days after the acute overdosage.

Treatment

In cases of acute poisoning, patients should be carefully monitored for some time to take account of the delayed onset of symptoms.

In acute poisoning the stomach should be emptied by administration of multiple dose activated charcoal.

Treatment is symptomatic and supportive. Respiration may require assistance. The circulation and blood pressure should be maintained and fluid and electrolyte imbalance corrected.

Haemodialysis or peritoneal dialysis may be of value when kidney function is compromised.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmaceutical category: agents for gout, without effect on uric acid metabolism

ATC code: M04AC01

Mechanism of action

Colchicine is an anti-inflammatory agent unique in its selective effectiveness against gout. An acute attack of gout apparently occurs as a result of an inflammatory reaction to crystals of mono-sodium urate that are deposited in the joint tissue from hyper-uric body fluids. The

inflammatory response involves local infiltration of granulocytes that phagocytise the urate crystals. In synovial tissues and in leucocytes 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 leucocytes directly and by diminishing phagocytosis, thereby interrupting the cycle of urate crystal deposition and inflammatory response that sustains the acute attack.

Other properties of colchicine, such as interaction with the microtubules, may also contribute to its action. The effect occurs about 12 hours after oral administration and is maximal after 1 - 2 days.

5.2. Pharmacokinetic properties

Absorption

Colchicine is rapidly and almost completely absorbed after oral administration. Maximum plasma levels are usually reached after 30 - 120 minutes. The terminal half-life is 3 to 10 hours.

Elimination

Plasma protein binding is about 30 %. Colchicine is partly converted in the liver and then partly excreted via the bile. It accumulates in white blood cells. Colchicine is excreted largely (80 %) in unchanged form and as a metabolite in the faeces, 10 – 20 % is excreted in the urine.

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

5.3 Preclinical safety data

Colchicine causes DNA damage *in vitro* and chromosome aberrations have been seen *in vivo*.

No toxicity data is known from preclinical research.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

CHOLDIX 0.5 mg tablets contain the following inactive ingredients:

Cellulose Microcrystalline

Sodium Starch Glycolate

Magnesium Stearate

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 25 °C.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container

CHOLDIX 0.5 mg is packed in printed 250 micron white opaque PVC film as the forming material and 25 µ aluminium foil as the lidding material. The blisters are packed in pre-printed cartons with package leaflet.

Pack sizes:

12's – 2 blisters of 6 tablets each

50's – 5 blisters of 10 tablets each

CHOLDIX 0.5 mg is packed in round wide mouth white opaque 30 ml HDPE container closed with white opaque 28 mm - 400 polypropylene child resistant closures with wad having induction sealing liner. The HDPE container isr packed in a pre-printed carton with package leaflet.

Pack sizes: 12's and 50's

Not all packs and pack sizes are necessarily marketed.

6.6. Special precautions for disposal <and other handling>

No special requirements.

7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

AUROGEN SA (Pty) Ltd

Woodhill Office Park, Building 1, First Floor

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12, 1448

Johannesburg

South Africa

8. REGISTRATION NUMBER

9. DATE OF FIRST AUTHORISATION

10. DATE OF REVISION OF TEXT