PROFESSIONAL INFORMATION

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

COLNOVA 0,5 colchicine, (tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0,5 mg colchicine.

Excipient with known effect:

COLNOVA 0,5 contains sugar (49 mg lactose monohydrate) per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

Off-white to light yellow coloured, round shaped, biconvex uncoated tablets debossed with 'C' on one side and ‘0,5’ on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COLNOVA 0,5 is indicated for the relief of acute attacks of gout.

4.2 Posology and method of administration

Acute attacks of gout in adult patients:

Take 0,5 to 1 mg (1 to 2 tablets) by mouth immediately, followed by 0,5 mg (1 tablet) 2 hourly until pain relief is obtained or until vomiting or diarrhoea occur.

A maximum dosage of 6 mg (six tablets) must not be exceeded.

A minimum of 3 days, but preferably 7 days, should elapse between courses of gout treatment with COLNOVA 0,5 to avoid cumulative toxicity.

Creatinine clearance:

GFR 10 to 50 mL/minute, 50 % of normal dose.

GFR less than 10 mL/minute, treatment with COLNOVA 0,5 must be avoided (see section 4.3).

Special populations

Elderly:

COLNOVA 0,5 should be given with caution to the elderly (see section 4.4).

Paediatric population

There are no data available.

COLNOVA 0,5 is not an analgesic medication and should not be used to treat pain from other causes.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to colchicine or to any of the excipients listed in section 6.1.
- COLNOVA 0,5 should not be used in patients undergoing haemodialysis since it cannot be removed by dialysis or exchange transfusion.
- In patients with severe renal impairment (creatinine clearance less than 10 mL/minute).
- Patients with severe hepatic impairment.
- In patients with blood disorders: myelosupression, leucopenia, granulocytopenia, thrombocytopenia and aplastic anaemia.
- Patients with renal or hepatic impairment should not be given COLNOVA 0,5 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 with COLNOVA 0,5 in therapeutic doses (see sections 4.5 and 4.4).
- Pregnancy and lactation. (see section 4.6)
- Women of childbearing potential unless using effective contraceptive measures.

4.4 Special warnings and precautions for use

Fatal overdoses

COLNOVA 0,5 potentially toxic, so it is important not to exceed the dose prescribed by a medical practitioner with the necessary knowledge and experience. (see section 4.2)

Colchicine as contained in COLNOVA 0,5 has a narrow therapeutic window. The administration should be discontinued if toxic symptoms such as nausea, vomiting, abdominal pain, diarrhoea occur. (see section 4.8)

Blood dyscrasias

COLNOVA 0,5 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 COLNOVA 0,5 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.

Hepatic and renal impairment

Patients with liver or renal impairment should be carefully monitored for adverse effects of COLNOVA 0,5 (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 COLNOVA 0,5 dosage or interruption of COLNOVA 0,5 treatment is recommended (see section 4.5).

Excipients

COLNOVA 0,5 contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take COLNOVA 0,5.

4.5 Interaction with other medicines and other forms of interaction

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 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 COLNOVA 0,5 dosage or an interruption of COLNOVA 0,5 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 COLNOVA 0,5 dosage is recommended when co-administered with a P-gp inhibitor and/or a strong CYP3A4 inhibitor. A 2-fold reduction in COLNOVA 0,5 dosage is recommended when co-administered with a moderate CYP3A4 inhibitor.

Given the nature of the side effects, caution is advised with concomitant administration of medicines 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 COLNOVA 0,5.

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 COLNOVA 0,5 with statins, fibrates, ciclosporin or digoxin.

Alcohol:

Concomitant use of COLNOVA 0,5 increases the risk of gastrointestinal disorders. Alcohol increases blood uric acid concentrations.

Non-steroidal anti-inflammatory drugs (NSAIDs):

Concomitant use may increase the risk of gastrointestinal symptoms.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

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

Pregnancy

Colchicine is genotoxic *in vitro* and *in vivo* and is teratogenic in animal studies (see section 5.3). COLNOVA 0,5 is therefore contraindicated in pregnancy (see section 4.3).

Breastfeeding

COLNOVA 0,5 is excreted in breast milk. Therefore, the use of COLNOVA 0,5 is contraindicated in women who are breastfeeding (see section 4.3).

Fertility

Colchicine administration in animals induces significant reductions in fertility.

4.7 Effects on ability to drive and use machines

No details are available regarding the influence of COLNOVA 0,5 on the ability to drive and use machines. However, patients should not drive, use machinery or perform any tasks that require concentration until they are certain that COLNOVA 0,5 do not adversely affect their ability to do so safely (see section 4.8).

4.8 Undesirable effects

a) Summary of safety profile

COLNOVA 0,5 frequently causes nausea, vomiting, abdominal pain and diarrhoea.

Tabulated summary of adverse reactions:

System organ class *a.*	**Adverse reaction**	**Frequency**
Blood and lymphatic system disorders	Bone marrow suppression with, agranulocytosis, aplastic anaemia, thrombocytopenia, leucopenia, neutropenia*	*Unknown frequency*
Nervous system disorders	Peripheral neuritis, peripheral neuropathy	*Unknown frequency*
Vascular disorders	Hypotension (with large doses)	*Unknown frequency*
Gastrointestinal system disorders	Abdominal pain, nausea, vomiting and diarrhoea**	*Frequent*

	Burning of the throat	*Less frequent*
	Profuse diarrhoea, gastrointestinal haemorrhage	*Unknown frequency*
Hepato-biliary disorders	Hepatic damage, hepatotoxity	*Unknown frequency*
Skin and subcutaneous tissue disorders	Urticaria, morbilliform eruptions	*Less frequent*
	Burning of the skin, skin rashes, alopecia	*Unknown frequency*
Musculoskeletal and connective tissue disorders	Myopathy and rhabdomyolysis	*Unknown frequent*
Renal and urinary disorders	Renal damage and dehydration	*Unknown frequency*
Reproductive system and breast disorders	Amenorrhoea, dysmenorrhoea, oligospermia, reversible azoospermia	*Unknown frequency*

Description of selected adverse reactions

* Larger doses may cause profuse diarrhoea, gastrointestinal haemorrhage, skin rashes and renal damage. Bone marrow depression with agranulocytosis, thrombocytopenia and aplastic anaemia have occurred on prolonged treatment, as well as peripheral neuritis, myopathy, rashes, and alopecia.

** COLNOVA 0,5 should be withdrawn or the dose reduced if gastrointestinal side effects occur.

Reporting of suspected adverse reactions

Reporting 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 Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Colchicine such as COLNOVA 0,5 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 COLNOVA 0,5 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 medicine 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.

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. Doses may be repeated every 4 hours in both adults and children, for those who ingested more than 300 microgram/kg, provided they are not vomiting.

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.

Patients should be monitored for at least 6 hours after ingestion, or 12 hours if they have taken more than 300 microgram/kg. Asymptomatic patients may then be discharged, with advice to return if gastrointestinal symptoms appear.

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

A 3.3 Anti-gout preparations

Pharmacotherapeutic group: Preparations for gout, with no effect on uric acid metabolism. ATC code: M04AC01

Colchicine is an anti-inflammatory medicine against gout. Colchicine diminishes lactic acid production by leucocytes directly and diminishes phagocytosis.

5.2 Pharmacokinetic properties

Absorption

Colchicine is rapidly, but variable absorbed after oral administration. Peak plasma concentrations are seen between 0,5 to 2 hours after administration.

Distribution

Plasma protein binding is 50 %. The formation of colchicine-tubulin complexes in many tissues contributes to its large volume of distribution. There is significant enterohepatic circulation. High concentrations of colchicine are seen in the kidney, liver, and spleen, but it apparently is largely excluded from heart, skeletal muscle and brain tissue.

Biotransformation

The exact metabolism of colchicine in humans is unknown, but *in vitro* studies indicate that it may undergo oxidative demethylation by CYP3A4. Metabolism may involve deacetylation in the liver. The plasma half-life is approximately 9 hours. Other CYP3A4 substrates have been associated with an increase in colchicine plasma $t_{½}$ and the emergence of colchicine toxicity.

Elimination

Urinary excretion is 10 % to 20 %, but increases with liver disease. The plasma $t_{½}$ of colchicine is approximately 9 hours, but colchicine can be detected in leukocytes and in the urine for at least 9 days after a single intravenous dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Intragranular ingredients:

Lactose monohydrate

Microcrystalline Cellulose

Extragranular ingredients:

Magnesium Stearate

Sodium Starch Glycolate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the tablets in the blisters until required for use.

6.5 Nature and contents of container

COLNOVA 0,5 tablets are packaged in white opaque PVC film - Aluminium foil blister.

COLNOVA 0,5 tablets packed in above blister will be further packed in pre-printed carton.

Blister pack sizes: 12’s: containing 2 blisters of 6 tablets each.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novagen Pharma (Pty) Ltd

Office 2

100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

Irene

Pretoria

0157

8. REGISTRATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 April 2023

10. DATE OF REVISION OF THE TEXT

04 April 2023