1.3.1.1 Professional Information for NOCOMYPRO

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

NOCOMYPRO 400 mg/325 mg, film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Ibuprofen 400 mg

Paracetamol 325 mg

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Orange coloured, oval, film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NOCOMYPRO is indicated for the relief of mild to moderate pain of inflammatory origin or non-inflammatory origin with or without fever.

4.2 Posology and method of administration

Posology

DO NOT EXCEED THE RECOMMENDED DOSE.

Use the lowest effective dose for the shortest possible duration of treatment.

Not recommended for children under twelve years.

Adults and children over 12 years: 2 tablets every 4 hours when necessary. Do not exceed 6 tablets in 24 hours. Tablets are to be taken with food or after meals with sufficient water.
If taking NOCOMYPRO of pain and the pain persists for longer than 7 days, or if taking NOCOMYPRO for fever and the fever persists for longer than 3 days or if the condition deteriorates or new symptoms develop, a re-evaluation of the condition is required by the doctor.

Paediatric population

The safety and efficacy of NOCOMYPRO in children under 12 years of age have not yet been established.

Method of administration

For oral administration.

4.3 Contraindications

- Hypersensitivity to ibuprofen, paracetamol or to any of the excipients listed in section 6.1.
- Avoid use of NSAIDs in women around 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/foetal renal dysfunction and premature closure of the foetal ductus arteriosus.
- NOCOMYPRO is contraindicated in heart failure.
- History of gastrointestinal perforation, ulceration, or bleeding (PUBs) related to previous NSAIDs, including NOCOMYPRO.
- Active or history of recurrent ulcer/haemorrhage/perforations.

- Patients sensitive to aspirin or another non-steroidal anti-inflammatory medicine.
- Uncontrolled asthma or bronchospasm.
- Nasal polyps associated with aspirin-induced bronchospasm.
- Patients with bleeding disorders.
- Severe liver impairment.
- Renal impairment.
- Pregnancy and lactation.
- Patients who are receiving coumarin-anticoagulants.

4.4 Special warnings and precautions for use

This product contains paracetamol which may be fatal in overdose or suspected overdose and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or Poison Centre must be contacted immediately.

Dosages of paracetamol in excess of those recommended may cause severe liver damage.

NOCOMYPRO should be used with caution in the following conditions:

- Alcoholism or impaired liver function - Increased risk of hepatotoxicity.
- Renal function impairment - Increased risk of adverse effects with prolonged use of high doses, occasional use is acceptable.

The antipyretic, analgesic and anti-inflammatory action of ibuprofen may mask symptoms of the occurrence or worsening of infection.

NOCOMYPRO should be used with caution in the following:

- In patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NOCOMYPRO therapy. In view of NOCOMYPRO's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.
- In patients with significant risk factors for cardiovascular events (e.g., hypertension, hyperlipidaemia, diabetes mellitus, smoking) and should only be treated with diclofenac after careful consideration.
- Inflammatory or ulcerative disease of the upper or lower gastrointestinal tract.
- Asthma - May be exacerbated.
- Allergic conditions - Possibility of cross sensitivity.
- Anaemia - May be exacerbated.
- Bleeding disorders - Increased risk of hepatotoxicity.
- Renal function impairment - Renal failure may be provoked, especially in patients with pre-existing renal impairment.

Avoid alcohol: Increased risk of liver toxicity, especially in alcoholics with high doses and prolonged use.

Diabetic patients: May experience false results with blood glucose tests.

Elderly patients: The elderly has an increased frequency of adverse reactions to NSAIDs including NOCOMYPRO, especially hepatic or renal effects and gastrointestinal perforation, ulceration, and bleeding (PUBs) which may be fatal.

Gastrointestinal:

- The risk of gastrointestinal perforation, ulceration, or bleeding (PUBs) is higher with increasing doses of NOCOMYPRO in patients with a history of ulcers, and the elderly.
- When gastrointestinal bleeding or ulceration occurs in patients receiving NOCOMYPRO treatment with NOCOMYPRO should be stopped.
- NOCOMYPRO should be given with caution to patients with a history of gastrointestinal disease (e.g., ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated.

Skin reactions: Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. NOCOMYPRO should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Surgery: Possible enhanced bleeding if surgery is required.

Foetal Toxicity:

Regular use of NSAIDs such as NOCOMYPRO during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus *in utero*, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed, and its duration increased.

Limit use of NSAIDs, including NOCOMYPRO, between 20 to 30 weeks of pregnancy due to the risk of oligohydramnios/foetal renal dysfunction. Avoid use of NSAIDs in women around 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/foetal renal dysfunction and premature closure of the foetal ductus arteriosus.

If NSAID treatment is necessary between 20 weeks and 30 weeks gestation, limit NOCOMYPRO use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if NOCOMYPRO treatment extends beyond 48 hours. Discontinue NOCOMYPRO if oligohydramnios occurs and follow up according to clinical practice.

4.5 Interactions with other medicines and other forms of interaction

- Hepatotoxic medicines: Increased risk of hepatotoxicity.
- Enzyme inducing medicines: Increased risk of hepatotoxicity. Possible decrease in therapeutic effects of paracetamol.
- Metoclopramide: Absorption of paracetamol may be accelerated.
- Cholestyramine: Absorption of paracetamol is reduced if given within one hour of cholestyramine.
- Anticoagulants: NOCOMYPRO may enhance the effects of anti-coagulants such as warfarin and the possibility of gastrointestinal bleeding.
- Alcohol, corticosteroids, clopidogrel, ticlopidine, bisphosphonates, pentoxifylline: Increased risk of gastrointestinal bleeding and ulceration.
- Antidiabetic agents: Hypoglycaemic effects of these medicines may be increased.
- Digoxin: Increase in serum digoxin concentrations.
- Lithium: Increase in the steady-state concentration of lithium.
- Methotrexate: Increased and prolonged methotrexate plasma concentration and increased risk of methotrexate toxicity.
- Nephrotic medicines e.g., ciclosporin: Increased risk of nephrotoxicity.
- Antihypertensives or diuretics: Reduction or reversal of the antihypertensive effect may occur.
- Bone marrow depressants: The leucopenic and/or thrombocytopenic effects of these medicines may be increased.
- Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (PUBs).
- Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of

gastrointestinal bleeding.

- NSAIDs: use of two or more NSAIDs concomitantly could result in an increase in side effects.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy in pregnancy have not been established.

Use of NSAIDs, including NOCOMYPRO, can cause premature closure of the foetal ductus arteriosus and foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, the use of NOCOMYPRO dose and duration between 20 and 30 weeks of gestation should be limited and avoided at around 30 weeks of gestation and later in pregnancy.

Breastfeeding

Safety and efficacy in lactation have not been established.

Fertility

No information available.

4.7 Effects on ability to drive and use machines

No information available.

Refer to section 4.8.

4.8 Undesirable effects

a. Summary of the safety profile

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal. Nausea, vomiting, diarrhoea, flatulence,

constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastritis.

b. Tabulated summary of adverse reactions

A tabulated summary of undesirable effects has been included for ibuprofen and paracetamol (in combination) below. Adverse reactions are listed by system organ class.

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Blood and lymphatic system disorders	Less frequent	Agranulocytosis, thrombocytopaenia, anaemia, neutropenia, eosinophilia.
Nervous system disorders	Frequent	Dizziness.
	Less frequent	Nervousness, headache, tinnitus, depression, drowsiness, insomnia.
Eye disorders	Less frequent	Blurred vision, changes in visual colour perception and other toxic amblyopia.
Cardiac disorders	Less frequent	Tachycardia, flushing, increase in blood pressure/ hypertension, heart failure.
Gastrointestinal Disorders	Frequent	Nausea, abdominal pain, vomiting, diarrhoea, flatulence, constipation, dyspepsia, peptic ulceration, perforation, or gastrointestinal bleeding, melena, haematemesis gastritis.
	Frequency unknown	Ulcerative stomatitis, exacerbation of colitis and Crohn's disease.
Hepatobiliary disorders	Less frequent	Hepatitis.
Skin and subcutaneous	Frequency unknown	Allergic dermatitis, erythema multiforme, bullous reactions including Stevens-Johnson syndrome

tissue disorders		and toxic epidermal necrolysis.
Renal and urinary disorders	Less frequent	Oedema, impairment of renal function, acute reversible renal impairment.
	Frequency unknown	Interstitial nephritis and nephritic syndrome.
General disorders and administration site conditions	Less frequent	Hypersensitivity reactions (fever, rashes, hepatotoxicity, and aseptic meningitis).

Post marketing experience

No information available.

c. Description of selected adverse reactions

No information available.

d. Paediatric population

The safety and efficacy of NOCOMYPRO in children under 12 years of age have not yet been established (see section 4.2).

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 professionals 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

Paracetamol:

Prompt treatment is essential. In the event of an overdosage, consult a doctor immediately, or take the person to the nearest hospital directly. A delay in starting treatment may mean that the antidote is given too late to be effective. Evidence of liver damage is often delayed until after the time for the effective treatment has lapsed. Specialised treatment is essential as soon as possible. Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses (greater than 5 to 10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of medicines that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.

Symptoms of paracetamol overdose

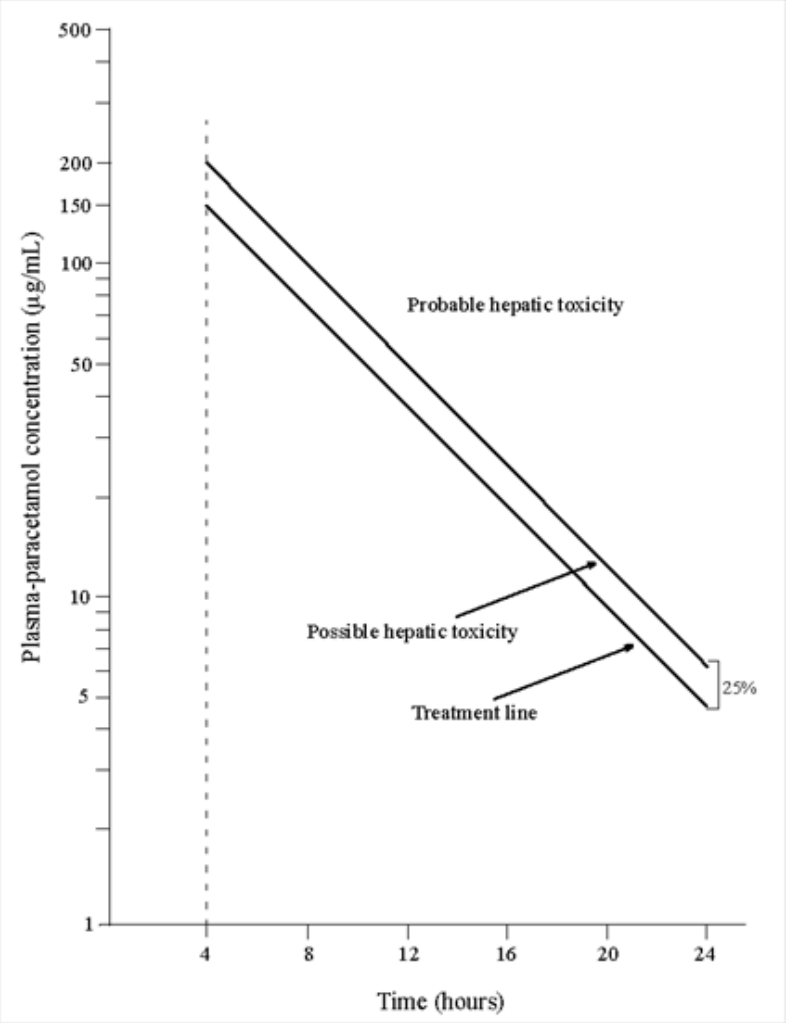
- Symptoms of paracetamol overdosage in the first 24 hours include pallor, nausea, vomiting, anorexia, and possibly, abdominal pain. Mild symptoms during the first two days of acute poisoning do not reflect the potential seriousness of the overdosage.
- Liver damage may become apparent 12 to 48 hours later, or after ingestion initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of the prothrombin time. Liver damage may lead to encephalopathy, coma, and death.
- Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac arrhythmias have been reported. Nausea, vomiting, anorexia, and abdominal pain may persist for a week or more. Cerebral oedema and nonspecific myocardial depression have also occurred.

Treatment of paracetamol overdosage:

- Although evidence is limited, it is recommended that any adult person who has ingested 5 to 10 grams or more of paracetamol (or a child who has had more than 140 mg/kg) within

the preceding four hours, should have the stomach emptied by gastric lavage (emesis may be adequate for children) and a single dose of 50 g activated charcoal given via the lavage tube. Ingestion of amounts of paracetamol smaller than this may require treatment in patients susceptible to paracetamol poisoning (see above). In patients who are stuperose or comatose endotracheal intubation should precede gastric lavage in order to avoid aspiration.

- Specialised therapy with an antidote such as acetylcysteine or methionine may be necessary. If decided upon, acetylcysteine should be administered IV as soon as possible.
- N-Acetylcysteine: N-Acetylcysteine should be administered to all cases of suspected overdose as soon as possible, preferably within 8 hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken.
- IV: An initial dose of 150 mg/kg in 200 mL dextrose injection, given intravenously over 15 minutes, followed by an intravenous infusion of 50 mg/kg in 500 mL of dextrose injection over the next 4 hours and then 1 000 mL dextrose injection over the next 16 hours. The volume of intravenous fluids should be modified for children.
- Orally: Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administered initially, followed by 70 mg/kg every 4 hours for 17 doses.
- If activated charcoal is used, then it should be removed by gastric lavage as it may interfere with the absorption of orally administered acetylcysteine and decrease the efficacy.
- A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdosage. Levels done before four hours, unless high, may be misleading. Patients at risk of liver damage, and hence requiring continued treatment with N-acetylcysteine can be identified according to their plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the normogram below. The nomogram should be used only in relation to a single acute ingestion.



- Those whose plasma paracetamol levels are above the “normal treatment line”, should continue N-acetylcysteine treatment with 100 mg/kg IV over sixteen hours repeatedly until recovery. Patients with increased susceptibility to liver damage as identified above, should continue treatment if concentrations are above the “high risk treatment line”. Prothrombin index correlates best with survival.
- Monitor all patients with significant ingestions for at least ninety-six hours.

Ibuprofen

Symptoms of ibuprofen overdosage:

- Gastrointestinal symptoms (e.g., abdominal pain, nausea, vomiting), central nervous system symptoms (e.g., lethargy, drowsiness), gastrointestinal haemorrhage, acute renal failure, convulsions and coma (see section 4.8).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.8 Analgesic combinations.

Mechanism of action

Paracetamol has analgesic and antipyretic effects. Ibuprofen has analgesic, antipyretic and anti-inflammatory activities. Ibuprofen inhibits platelet aggregation.

5.2 Pharmacokinetic properties

Paracetamol:

Absorption following oral administration is well and almost complete. Paracetamol is metabolized in the liver primarily by conjugation.

Paracetamol has a half-life of 1 to 4 hours, time to peak concentration of 0,5 to 2 hours, time to peak effect of 1 to 3 hours and the duration of action of 3 to 4 hours.

Paracetamol is renally excreted primarily as metabolites and 3 % of a dose may be excreted unchanged.

Ibuprofen:

Well absorbed after oral administration. Onset of action for pain relief is 30 minutes and time to peak effect for fever is 2 to 4 hours. The half-life of ibuprofen is about 2 hours and the duration of action for fever is 6 to 8 hours or more and is 4 to 6 hours for pain. More than 90 % of an ingested dose is excreted in the urine as metabolite or their conjugates. Protein binding of ibuprofen is more than 95 %.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate (Dihydrate);

Opadry 06G53189 orange (containing hypromellose, macrogol/PEG 6000, polyethylene glycol,

sodium laurilsulfate, Sunset Yellow and titanium dioxide);

Povidone (PVPK K 30);

Pregelatinised starch (starch 1500);

Purified talc.

6.2 Incompatibilities

No data available.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 30 °C, protected from light and moisture.

6.5 Nature and contents of container

Carton containing 30, 60 or 100 tablets in blister strips of 10 tablets each.

HDPE bottle containing 500 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

Address

1 New Road

Erand Gardens

Midrand

1685

P.O. Box

Private Bag X69

Bryanston, 2021

8. REGISTRATION NUMBER(S)

57/2.8/0407

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 03 August 2022

10. DATE OF REVISION OF THE TEXT

TBC