## 1.3.1.1. PROFESSIONAL INFORMATION FOR NUROFEN PLUS

## SCHEDULING STATUS

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## 1. NAME OF THE MEDICINE

**NUROFEN PLUS** tablets

## 2. QUALITITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains, Ibuprofen 200 mg and Codeine Phosphate 12,8 mg

Sugar free

For full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Tablets

A white film-coated biconvex capsule-shaped tablet, embossed with the logo "N+" on the one side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications:

NUROFEN PLUS is indicated for the relief of mild to moderate pain of inflammatory origin with or without fever.

### 4.2 Posology and method of administration

Use the lowest effective dose for the shortest possible duration of treatment (see section 4.4).

**Posology**

**Adults**

One or two tablets every four hours and not more than six tablets per twenty- four hours. Consult your doctor if symptoms persist, worsen or if new symptoms occur.

Do not take for longer than 5 days, without consulting your doctor.

**Paediatric population**

Not recommended for children under twelve years of age.

**Method of administration**

For oral administration.

**4.3 Contra-indications**

- NUROFEN PLUS should not be given to patients with existing or a history of gastrointestinal bleeding or perforation (PUBs) related to previous NSAID use. Active or history of recurrent ulcer, haemorrhage or perforations.
- Hypersensitivity to Ibuprofen, Codeine or to any of the constituents, aspirin or any other non-steroidal anti-inflammatory drugs (NSAIDs), or codeine.
- Patients with a history of bronchospasm, rhinitis, angioedema, urticaria, associated with aspirin or other NSAIDs.
- Use of NSAIDs is contra-indicated in patients with heart failure, renal failure or hepatic failure.
- Respiratory depression and chronic constipation.
- Concomitant treatment with Monoamine Oxidase Inhibitors (MAOIs) or within 14 days of stopping treatment (see section 4.5).

- In all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions and increased susceptibility to respiratory problems.
- In children under the age of 12 years.
- In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers

NUROFEN PLUS is contraindicated in pregnancy and breastfeeding (see section 4.6).

**4.4 Special warnings and precautions for use**

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

- Caution is required in patients with a history of hypertension as fluid retention and oedema have been reported in association with NSAIDs therapy.
- **Elderly:** The Elderly have an increased frequency of adverse reactions to NSAID's, especially gastrointestinal bleeding and perforation (PUBs) which may be fatal. The risk of gastrointestinal bleeding or perforation (PUBs) is higher with increasing doses of NSAIDs, in patients with a history of ulcers, and the elderly.
- When gastrointestinal bleeding or ulceration occurs in patients receiving NSAIDs, treatment with NSAIDs should be stopped.
- **Respiratory:** Bronchospasm may be precipitated in patients suffering from or with a history of bronchial asthma or allergic disease.
- **Other NSAIDs:** The use of Ibuprofen with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

- **SLE and mixed connective tissue disease:** Systemic lupus erythematosus and mixed connective tissue disease, due to increased risk of aseptic meningitis.
- **Cardiovascular and cerebrovascular effects:** Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension as fluid retention, hypertension and oedema have been reported in association with NSAIDs therapy. Clinical trial and epidemiological data suggest that the use of Ibuprofen, particularly at high doses (2400 mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose Ibuprofen (e.g. ≤ 1200 mg daily) is associated with an increased risk of myocardial infarction.

**Renal:**

Renal impairment as renal function may deteriorate. There is a risk of renal impairment in dehydrated children and adolescents.

Severe hypokalaemia and renal tubular acidosis have been reported due to prolonged use of ibuprofen at higher than recommended doses. This risk is increased with the use of codeine/ibuprofen as patients may become dependent on the codeine component (see warning on Opioid use disorder, section 4.8 and section 4.9). Presenting signs and symptoms included reduced level of consciousness and generalised weakness. Ibuprofen induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis.

Tolerance, physical and psychological dependence and opioid use disorder (OUD) may develop upon repeated administration of opioids such as codeine. Abuse or intentional misuse of NUROFEN PLUS may result in overdose and/or death. Serious clinical outcomes, including

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fatalities, have been reported in association with abuse and dependence with codeine/ibuprofen combinations, particularly when taken for prolonged periods at higher than recommended doses. These have included reports of gastrointestinal perforations, gastrointestinal haemorrhages, severe anaemia, renal failure, renal tubular acidosis and severe hypokalaemia associated with the ibuprofen component.

Patients should be informed about the risks and signs of OUD as well as serious clinical outcomes. If these signs occur, patients should be advised to contact their doctor.

Withdrawal symptoms, such as restlessness and irritability may occur once the treatment is stopped.

- **Hepatic:** Hepatic dysfunction.

- **Impaired female fertility** (see section 4.6).

- **Gastrointestinal effects**: NSAIDs should be given with caution to patients with a history of gastrointestinal disease (e.g. Crohn's disease, hiatus hernia, gastro- oesophageal reflux disease as the condition may be exacerbated.

  Gastrointestinal bleeding, ulceration or perforation which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events. The risk of GI bleeding, ulceration or perforation is higher with increasing NSAIDs doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly.

  These patients should commence treatment on the lowest dose available. Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially

GI bleeding) particularly in the initial stages of treatment. When GI bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn.

Caution should be advised in patients receiving concomitant medications which could increase the risk of gastrotoxicity, ulceration or bleeding, such as oral corticosteroids, or anticoagulants such as warfarin, selective serotonin reuptake inhibitors or anti-platelet agents (see section 4.5 Interactions).

- **Dermatological effects:** Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. NUROFEN PLUS use should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

  NUROFEN PLUS can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When this medicine is administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

Do not take concurrently with any other Codeine containing compounds.

**Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS)**

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Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as NUROFEN PLUS. Some of these events have been fatal or life-threatening. DRESS typically, althought not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. The clinical manifestations may include hepatitis, nephritis, haematologocal abnormalities, myocarditis, or myositis. Somestimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue NUROFEN PLUS and evaluate the patient immediately.

- **Sleeping disorder where your body stops and starts your breathing in a way that disrupts your sleep:**

  Opioids such as NUROFEN PLUS can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper.

- **Increased sensitivity to pain:**

  Hyperalgesia has been reported with the use of opioids, particularly following long-term use and/or at high doses. Hyperalgesia may resolve with opioid dose reduction, discontinuation or switching to a different opioid.

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- Care is advised in the administration of Codeine to patients with hypotension, hypothyroidism, adrenocortical insufficiency, shock, obstructive bowel disorders, acute abdominal conditions (e.g. peptic ulcer), recent gastrointestinal surgery, gallstones, myasthenia gravis or convulsions and also in patients with a history of drug abuse.
- Elderly patients may metabolise or eliminate opioid analgesics more slowly than younger adults. Codeine should be used with caution in the elderly and debilitated patients as they may be more susceptible to the respiratory depressant effects.
- Prolonged regular use of Codeine, except under medical supervision, may lead to physical and psychological dependence (addiction) and result in withdrawal symptoms, such as restlessness and irritability once the drug is stopped.
- **CYP2D6 metabolism:** Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained.

  Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.

  General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression which may be life-threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

| **Population** | **Prevalence %** |
|---|---|

| | |
|---|---|
| African/Ethiopian | 29 % |
| African American | 3,4 % to 6,5 % |
| Asian | 1,2 % to 2 % |
| Caucasian | 3,6 % to 6,5 % |
| Greek | 6,0 % |
| Hungarian | 1,9 % |
| Northern European | 1 to 2 % |

**Paediatric population:**

- ***Post-operative use in children:*** there have been reports in the published literature that codeine given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea led to life-threatening adverse events including death (see section 4.3). All children received doses of codeine that were within the appropriate dose range; however, there was evidence that these children were either ultrarapid or extensive metabolisers in their ability to metabolise codeine to morphine.
- ***Children with compromised respiratory function:*** codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity. Keep out of the sight and reach of children.

**4.5 Interactions with other medicines and other forms of interaction:**

NUROFEN PLUS should not be taken without consulting a doctor or pharmacist if you are presently taking coumarin anticoagulants as it may enhance the effects of the anticoagulants such as Warfarin.

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NUROFEN PLUS should not be taken without consulting a doctor or pharmacist if you are presently taking antihypertensives, lithium, monoamine oxidase inhibitors, methotrexate and when taking other pain relievers such as aspirin and other NSAIDs.

Interaction between NSAIDs and corticosteroids can cause an increased risk of gastrointestinal ulceration of bleeding (PUBs).

Interaction between NSAIDs and antiplatelet agents and selective serotonin reuptake inhibitors (SSRI's) can increase the risk of gastrointestinal bleeding. Use of two or more NSAID's concomitantly could result in an increase in side effects.

Avoid alcohol- may cause drowsiness. If affected do not drive or operate machinery.

The following drug-drug interactions are known to occur in association with the Ibuprofen active substance in the product:

**The product should be avoided in combination with:**

- **Acetylsalicylic acid (Aspirin):** Unless low-dose acetylsalicylic acid (Aspirin) (not above 75 mg daily) has been advised by a doctor, as this may increase the risk of adverse reactions. Experimental data suggest that Ibuprofen may inhibit the effect of low dose acetylsalicylic acid (aspirin) platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular Ibuprofen use, and no clinically relevant effect is considered to be likely for occasional Ibuprofen use.
- **Other NSAIDs including cyclooxygenase-2 selective inhibitors:** Avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse effects

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- Monoamine Oxidase Inhibitors (MAOIs): CNS depression or excitation may occur if Codeine is given to patients receiving monoamine oxidase inhibitors, or within two weeks of stopping treatment with them.

**The product should be used with caution in combination with:**

- **Anti-coagulants**: NSAIDs may enhance the effects of anti-coagulants, such as warfarin.
- **Antihypertensives (ACE inhibitors and Angiotensin II Antagonists) and diuretics:** NSAIDs may diminish the effects of these medicines ~~drugs~~. Diuretics can increase the risk of nephrotoxicity of NSAIDs.
- **Corticosteroids:** Increased risk of gastrointestinal ulceration or bleeding.
- **Anti-platelet medicines and selective serotonin reuptake inhibitors (SSRIs):** Increased risk of gastrointestinal bleeding.
- **Cardiac glycosides:** NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.
- **Lithium:** There is evidence for potential increases in plasma levels of lithium.
- **Methotrexate:** There is a potential for an increase in plasma levels of methotrexate.
- **Ciclosporin:** Increased risk of nephrotoxicity.
- **Mifepristone:** NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
- **Tacrolimus**: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
- **Zidovudine**: Increased risk of haematological toxicity when NSAIDs are given with Zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (positive) haemophiliacs receiving concurrent treatment with zidovudine and Ibuprofen.

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- **Quinolone antibiotics:** Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

The following drug-drug interactions are known to occur in association with the Codeine active substance in the product:

- **Moclobemide:** Risk of hypertensive crisis.
- **Hydroxyzine**: Concurrent use of hydroxyzine (anxiolytics) with Codeine may result in increased analgesia as well as increased CNS depressant, sedative and hypotensive effects.
- **Central Nervous System Depressants**: The depressant effects of Codeine are enhanced by depressants of the central nervous system such as alcohol, anaesthetics, hypnotics, sedatives, tricyclic antidepressants or antipsychotics and phenothiazines.
- **Diuretics and Anti-hypertensives**: The hypotensive actions of diuretics and anti –hypertensive agents may be potentiated when used concurrently with opioid analgesics.
- **Antidiarrhoeal and anti-peristaltic agents**: Concurrent use of Codeine with antidiarrhoeal and anti-peristaltic agents such as loperamide and kaolin may increase the risk of severe constipation.
- **Antimuscarinics:** Concomitant use of antimuscarinics or medications with muscarinic action, e.g. atropine and some antidepressants may result in an increased risk of severe constipation which may lead to paralytic ileus and/or urinary retention.
- **Neuromuscular Blocking Agents:** The respiratory depressant effect caused by neuromuscular blocking agents may be additive to the central respiratory depressant effects of opioid analgesics.
- **Quinidine:** Quinidine can inhibit the analgesic effect of Codeine.
- **Mexiletine:** Codeine may delay the absorption of mexiletine and thus reduce the antiarrhythmic effect of the latter.

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- **Metoclopramide, cisapride and domperidone:** Codeine may antagonise the gastrointestinal effects of metoclopramide, cisapride and domperidone.
- **Cimetidine:** Cimetidine inhibits the metabolism of opioid analgesics resulting in increased plasma concentrations.
- **Naxolone:** Naxolone antagonises the analgesic, CNS and respiratory depressant effects of opioid analgesics. Naltrexone also blocks the therapeutic effect of opioids.
- **Interference with laboratory tests:** Opioid analgesics interfere with a number of laboratory tests including plasma amylase, lipase, bilirubin, alkaline, phosphatase, lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase. Opioids may also interfere with gastric emptying studies as they delay gastric emptying and with hepatobiliary imaging using technetium Tc 99m disofenin as opioid treatment may cause constriction of the sphincter of Oddi and increase biliary tract pressure.

### 4.6 Fertility, pregnancy and lactation

**Pregnancy**

The product is contraindicated throughout pregnancy.

*First trimester*

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies raise concern about an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1 %, up to approximately 1,5 %. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased

incidences of various malformations including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

*Second and Third trimester*

During the third trimester of pregnancy, prostaglandin synthesis inhibitors, may expose the foetus to:

- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)
- Renal dysfunction, which may progress to renal failure with oligo-hydroamniosis.

At the end of pregnancy, the mother and the neonate may be exposed to possible:

- Prolongation of bleeding time
- An anti-aggregating effect which may occur even at very low doses
- Inhibition of uterine contractions resulting in delayed or prolonged labour.

**Breast-feeding**

The product is contraindicated in breastfeeding.

At normal therapeutic doses Codeine and its active metabolite may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant which may be fatal.

**Fertility**

There is limited evidence that drugs which inhibit cyclo-oxygenase/ prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

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**4.7 Effects on ability to drive and use machines**

Opioid analgesics can impair mental function and cause blurred vision and dizziness. Rare side effects may include convulsions, hallucinations, blurred or double vision and orthostatic hypotension. Patients should be advised not to drive or operate machinery if affected.

**4.8 Undesirable effects**

*a) Summary of the safety profile*

Hypersensitivity reactions have been reported and these may consist of:

- Non-specific allergic reactions and anaphylaxis.
- Respiratory tract reactivity, e.g. asthma, aggravated asthma, bronchospasm, dyspnoea.
- Various skin reactions, e.g. pruritus, urticaria, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme). Regular prolonged use of codeine is known to lead to addiction and symptoms of restlessness and irritability may result when treatment is then stopped.

Prolonged use of a painkiller for headache can make them worse.

The list of the following adverse events relates to those experienced with Ibuprofen and Codeine at OTC doses (maximum 1200 mg Ibuprofen per day), in short-term use. In the treatment of chronic conditions, under long-term treatment, additional adverse events may occur.

Adverse events which have been associated with Ibuprofen and Codeine are given below, tabulated by system organ class and frequency.

Frequencies are defined as:

Very common (≥1/10); common (≥1/100 and <1/10); uncommon (≥1/1,000 and <1/100); rare (≥1/10,000 and <1/1,000); very rare (<1/10,000), and not known (cannot be estimated from the available data).

Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

*b) Tabulated summary of adverse reactions*

| **System Organ Class** | **Frequency** | **Adverse Events** |
|---|---|---|
| Blood and Lymphatic System Disorders | Very rare | Haematopoietic disorders[1] |
| Immune System Disorders | Uncommon | Hypersensitivity with urticaria and pruritus |
| | Very rare | Severe hypersensitivity reactions, including facial, tongue and throat swelling, dyspnoea, tachycardia, and hypotension (anaphylaxis, angioedema or severe shock) |
| Metabolism and nutrition disorders | Not known | Decreased appetite, hypokalaemia[9] |
| Psychiatric Disorders | Not known | Depression, hallucination, confusional state, dependence, mood altered, restlessness, nightmares |
| Nervous System Disorders | Uncommon | Headache |
| | Very rare | Aseptic meningitis[2] |

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|---|---|---|
| | Not known | Dizziness, drowsiness, convulsion, intracranial pressure increased, dyskinesia |
| Eye Disorders | Not known | Vision blurred, diplopia |
| Ear and Labyrinth disorders | Not known | Vertigo |
| Cardiac Disorders | Not known | Cardiac failure, oedema, bradycardia, palpitations[3] |
| Vascular Disorders | Not known | Hypertension, orthostatic hypotension[3] |
| Respiratory, Thoracic and Mediastinal Disorders | Not known | Respiratory tract reactivity comprising asthma, bronchospasm or dyspnoea.<br>Respiratory depression, cough suppression |
| Gastrointestinal Disorders | Uncommon | Abdominal pain, nausea and dyspepsia[4] |
| | Rare | Diarrhoea, flatulence, constipation, vomiting |
| | Very rare | Peptic ulcer, gastrointestinal perforation or gastrointestinal |

| | | |
|---|---|---|
| | | haemorrhage, melaena, and haematemesis[5].<br>Mouth ulceration and gastritis |
| | Not known | Exacerbation of colitis and Crohn's disease[6]<br>Dry mouth |
| Hepatobiliary Disorders | Very rare | Liver disorder |
| | Not known | Biliary colic |
| Skin and Subcutaneous Tissue Disorders | Uncommon | Various skin rashes |
| | Very rare | Bullous reactions, including Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis |

| | | |
|---|---|---|
| | Not known | Flushing<br>Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome) (see section 4.4)<br>Acute generalised exanthematous pustulosis (AGEP)<br>Photosensitivity reactions |
| Musculoskeletal and connective tissue disorders | Not known | Muscle rigidity |
| Renal and Urinary Disorders | Very rare | Acute renal failure[7] |
| | Not known | Ureteric colic, dysuria[8], renal tubular acidosis |
| General and Administration Site Conditions | Not known | Hypothermia, hyperhidrosis, irritability, fatigue, malaise |
| Investigations | Very rare | Haemoglobin decreased |

*c) Description of selected adverse reactions*

[1] Examples include anaemia, leukopenia, thrombocytopenia, pancytopenia and agranulocytosis. First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.

[2] Single cases have been reported very rarely. The pathogenic mechanism of drug-induced aseptic meningitis is not fully understood. However, the available data on NSAID-related aseptic meningitis points to a hypersensitivity reaction (due to a temporal relationship with medicine intake, and disappearance of symptoms after medicine discontinuation). In patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed (see section 4.4).

[3] Reported in association with NSAIDs treatment. Clinical trial and epidemiological data suggest that use of ibuprofen (particularly at high doses 2400mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

[4] The most commonly-observed adverse events are gastrointestinal in nature.

[5] Sometimes fatal, particularly in the elderly.

[6] See section 4.4.

[7] Especially in long-term use, associated with increased serum urea and oedema. Also includes papillary necrosis.

[8] Increased frequency, decrease in amount.

[9]Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of the ibuprofen component at higher than recommended doses due to dependence on the codeine component.

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**Post marketing experience:**

**Gastrointestinal disorders:**

*Rare*: increased risk of abdominal pain, including acute pancreatitis has been reported.

**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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

**4.9 Overdose**

Overuse of this product, defined as consumption of quantities in excess of the recommended dose, or consumption for a prolonged period, may lead to physical or psychological dependency. Symptoms of restlessness and irritability may result when treatment is stopped.
In children ingestion of more than 400 mg Ibuprofen per kg of bodyweight may cause symptoms. In adults the dose response effect is less clear cut. The half-life of Ibuprofen in overdose is 1,5-3 hours.
Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see section 4.4 and section 4.8).

**Symptoms**

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system,

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manifesting as drowsiness, occasionally excitation and disorientation, respiratory depression, or coma. Co-ingestion of other sedative agents, including alcohol, may exacerbate effects on the central nervous system. Occasionally patients develop convulsions. The pupils may be pin-point in size. Hypotension and tachycardia are possible but unlikely. In serious poisoning metabolic acidosis may occur and the prothrombin time/ INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur. Exacerbation of asthma is possible in asthmatics.

**Management**

Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount, including more than 350 mg Codeine or for a child, more than 5 mg Codeine per kg of bodyweight. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma. Give naloxone if coma or respiratory depression is present. Naloxone is a competitive antagonist and has a short half- life so large and repeated doses may be required in a seriously poisoned patient. Observe for at least four hours after ingestion, or eight hours if a sustained release preparation has been taken.

## 5. PHARMACOLOGICAL PROPERTIES:

### 5.1 Pharmacodynamic properties

**Pharmacological classification:** A 2.7 Antipyretics or antipyretic and anti-inflammatory analgesics

**Pharmacotherapeutic group:** Ibuprofen, combinations; ATC Code: M01 AE51

NUROFEN PLUS tablets have an analgesic, anti-inflammatory and antipyretic action.

Ibuprofen is a propionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans, Ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, Ibuprofen reversibly inhibits platelet aggregation.

Codeine is a centrally acting weak analgesic. Codeine exerts its effect through μ opioid receptors, although Codeine has low affinity for these receptors, and its analgesic effect is due to its conversion to morphine. Codeine, particularly in combination with other analgesics such as paracetamol, has been shown to be effective in acute nociceptive pain.

**5.2 Pharmacokinetic properties**

Ibuprofen is rapidly absorbed following administration and is rapidly distributed throughout the whole body. The excretion is rapid and complete via the kidneys.

Maximum plasma concentrations are reached 45 minutes after ingestion if taken on an empty stomach. When taken with food, peak levels are observed after 1 to 2 hours. These times may vary with different dosage forms.

The half-life of Ibuprofen is about 2 hours.

Codeine phosphate is well absorbed after oral administration, producing peak plasma concentrations in about one hour. The plasma half-life is between 3 and 4 hours, excretion being mainly in the urine.

**5.3 Preclinical safety**

Not applicable

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

**Tablet core**

Hypromellose

Microcrystalline cellulose

Sodium starch glycolate

Pregelatinized starch

**Film coating**

Hypromellose

Opaspray white M-1-7-111B

Talc

**Composition of Opaspray white M-1-7-111B**

Hypromellose

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

36 months

**6.4 Special precautions for storage**

Store at or below 25°C.

**6.5 Nature and contents of container:**

Blister packs consisting of an opaque PVC/PVdC laminate heat sealed to aluminium foil containing 24 tablets in a cardboard container.

### 6.6 Special precautions for disposal

Not applicable

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Reckitt Benckiser Pharmaceuticals (Pty) Ltd

8 Jet Park Road

Elandsfontein

1601

## 8. REGISTRATION NUMBER

37/2.7/0666

## 9. DATE OF FIRST OF AUTHORISATION/RENEWAL OF THE AUTHORISATION

03 June 2005

## 10. DATE OF REVISION OF THE TEXT

05 March 2025

Namibia: 13/27/0168 NS2

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