1. NAME OF THE MEDICINAL PRODUCT

1.1 Name of Medicinal Product

NURODOL FORTE

(Caffeine, Ibuprofen and Paracetamol Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:

Ibuprofen BP	400 mg
Paracetamol BP	500 mg
Caffeine (Anhydrous) BP	30 mg
Excipients	q.s.

Colour: Tartrazine

3. PHARMACEUTICAL FORM

Uncoated Tablets for oral use

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the temporary relief of mild to moderate pain associated with migraine, headache, backache, period pain, dental pain, rheumatic and muscular pain, pain of non-serious arthritis, cold and flu symptoms, sore throat and fever. This product is especially suitable for pain which requires stronger analgesia like combination of caffeine, ibuprofen and paracetamol.

4.2 Posology and method of administration

Route of administration: Oral

The lowest effective dose should be used for the shortest time necessary to relieve symptoms. The patient should consult a doctor if the symptoms persist or worsen or if the product is required for more than 3 days.

Adults: One tablet to be taken up to three times per day with water. Leave at least six hours between doses.

If the one tablet dose does not control symptoms, a maximum of two tablets may be taken up to three times a day. Leave at least six hours between doses.

Do not take more than three tablets (1200mg Ibuprofen, 1500mg Paracetamol & 90mg Caffeine) in any 24 hours period.

To minimise side effects, it is recommended that patients take Fenbase extra with food.

Elderly: No special dosage modifications are required (see section 4.4).
The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used for the shortest possible duration. The patient should be monitored regularly for gastrointestinal bleeding during NSAID therapy.
Not for use by children under 12 years of age or as directed by the physician.

4.3 Contra-indications

This product is contraindicated:

- In patients with a known hypersensitivity to Caffeine, Ibuprofen and Paracetamol or any other excipients.
- In patients with a history of hypersensitivity reactions (e.g. bronchospasm, angioedema, asthma, rhinitis, or urticaria) associated with acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs).
- In patients with a history of, or an existing gastrointestinal ulceration/perforation or bleeding, including that associated with NSAIDs (see Section 4.4).
- Patients with defects in coagulation.
- In patients with severe hepatic failure, severe renal failure or severe heart failure (see Section 4.4).
- In concomitant use with other NSAID containing products, including cyclo-oxygenase-2 (COX-2) specific inhibitors and doses of acetylsalicylic acid above 75 mg daily – increased risk of adverse reactions (see Section 4.5).
- In concomitant use with other paracetamol-containing products – increased risk of serious adverse effects (see Section 4.5).

During the last trimester of pregnancy due to risk of premature closure of the fetus ductus arteriosus with possible pulmonary hypertension (see Section 4.6)

4.4 Special warnings and special precautions for use

The hazard of Paracetamol overdose is greater in patients with non-cirrhotic alcoholic liver disease. Immediate medical advice should be sought in the event of an overdose, even if the patient feels well, because of the risk of delayed, serious liver damage.
Undesirable effects may be minimised by using the lowest effective dose for the shortest

duration necessary to control symptoms (see Section 4.2, and gastrointestinal and cardiovascular risks below) and by patients taking the dose with food (see Section 4.2).

Elderly:

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see Section 4.2).

Caution is required in patients with certain conditions:

- Respiratory disorders:

  In patients suffering from, or with a history of, bronchial asthma or allergic disease NSAIDs have been reported to precipitate bronchospasm.

- Cardiovascular, renal and hepatic impairment:

  The administration of NSAIDs may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see Section 4.3).

- Cardiovascular and cerebrovascular effects:

  Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

  Clinical trial data suggest that 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 (e.g. myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤1200mg daily) is associated with an increased risk of myocardial infarction.

  Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration. Similar consideration should be made before initiating long-term treatment for patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

- Gastrointestinal bleeding, ulceration and perforation:
  Gastrointestinal (GI) bleeding, ulceration and 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 NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see Section 4.3) and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose acetylsalicylic acid, or other drugs likely to increase gastrointestinal risk (see below and 4.5).

  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.

  Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin selective serotonin-reuptake inhibitors or antiplatelet agents such as acetylsalicylic acid (see Section 4.5).
  When GI bleeding or ulceration occurs in patients receiving ibuprofen containing products, the treatment should be withdrawn.
  NSAIDs should be given with care to patients with a history of GI disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see Section 4.8).
- SLE and mixed connective tissue disease:
  In patient with systemic lupus erythematosus (SLE) and mixed connective tissue disease disorders there may be an increased risk of aseptic meningitis (see Section 4.8).

- Dermatological:
  Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see Section 4.8). 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. Use of this product should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

- Impaired female fertility:
  The use of the product may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of the product should be considered.

4.5 Interactions with other Drug products and other forms of interaction

Nurodol Forte (like any other paracetamol containing products) is contraindicated in combination with other paracetamol containing products – increased risk of serious adverse effects (see Section 4.3).

Nurodol Forte (like any other ibuprofen containing products and NSAIDs) is contraindicated in combination with:

- Acetylsalicylic acid, unless low-dose acetylsalicylic acid (not above 75 mg daily) has been advised by a doctor, as this may increase the risk of adverse reactions (see Section 4.3).
- Other NSAIDs including cyclo-oxygenase-2 selective inhibitors as these may increase the risk of adverse effects (see Section 4.3).

Nurodol Forte (like any other paracetamol containing products) should be used with caution in combination with:

- Chloramphenicol: Increased plasma concentration of chloramphenicol.
- Cholestyramine: The speed of absorption of paracetamol is reduced by cholestyramine. Therefore, cholestyramine should not be taken within one hour if maximal analgesia is required.
- Metoclopramide and Domperidone: The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.
- Warfarin: The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

Nurodol Forte (like any other ibuprofen containing products and NSAIDs) should be used with caution in combination with:

- Anticoagulants: NSAIDs may enhance the effects of anticoagulants, i.e. warfarin.
- Antihypertensives: NSAIDs may reduce the effects of these drugs.
- Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see Section 4.4).
- Acetylsalicylic acid: Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelets aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding the 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 use (see section 5.1)
- Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.
- Cyclosporine: Increased risk of nephrotoxicity.
- Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see Section 4.4).
- Diuretics: Reduced diuretic effect. Diuretics may increase the risk of nephrotoxicity of NSAIDs.
- Lithium: Decreased elimination of lithium.
- Methotrexate: Decreased elimination of methotrexate.
- Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.
- 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.
- Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
- Zidovudine: Increased risks of haematological toxicity with NSAIDS are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

4.6 Pregnancy and lactation

Pregnancy:

There is no experience of use of this product in humans during pregnancy.

Congenital abnormalities have been reported in association with NSAID administration in man; however these are low in frequency and do not appear to follow any discernible pattern. In view of the known effects of NSAIDs on the foetal cardiovascular system (risk of closure of ductus arteriosus), use in the last trimester is contraindicated. The onset of labour may be delayed and duration increased with an increased bleeding tendency in both mother and child (see Section 4.3). NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol use at the recommended dosage.

Therefore if possible, the use of this product should be avoided in the first six months of pregnancy and contraindicated in the last three months of pregnancy (see Section 4.3).

Lactation:

Ibuprofen and its metabolites can pass in very small amounts (0.0008% of the maternal dose) into the breast milk. No harmful effects to infants are known.
Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breastfeeding.

Therefore it is not necessary to interrupt breastfeeding for short-term treatment with the recommended dose of this product.

See Section 4.4 regarding female fertility.

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected patients should not drive or operate machinery.

4.8 Undesirable effects

Clinical trials with this product have not indicated any other undesirable effects other than those for ibuprofen or paracetamol alone.

The following table lists adverse effects from Pharmacovigilance data experienced by patients taking ibuprofen alone or paracetamol alone in short-term and long-term use.

Table 1

Blood and lymphatic system disorders	Very rare (≤1/10,000)	Haematopoietic disorders (agranulocytosis, anaemia, aplastic anaemia, haemolytic anaemia leucopenia, neutropenia, pancytopenia and thrombocytopenia). **First signs are**: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising and nose bleeding.
Immune system disorders	Very rare (≤1/10,000)	Hypersensitivity reactions have been reported. These may consist of non-specific allergic reactions and anaphylaxis. Severe hypersensitivity reactions. **Symptoms can include**: facial, tongue and larynx swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock).
Psychiatric disorders	Very rare (≤1/10,000)	Confusion, depression and hallucinations.
Nervous system disorders	Uncommon (≥1/1,000 to ≤1/100):	Headache and dizziness.
	Very rare (≤1/10,000)	Paraesthesia, optic neuritis and somnolence. Single cases of aseptic meningitis in patients with existing autoimmune disorders (such as systemic lupus erythematosus and mixed connective tissue disease) during treatment with ibuprofen, with **symptoms such as:** stiff neck, headache, nausea, vomiting, fever or disorientation have been observed (see Section 4.4).
Eye disorders	Very rare (≤1/10,000)	Visual disturbance.
Ear and	Very rare	Tinnitus and vertigo.

labyrinth disorders	(≤1/10,000)	
Cardiac disorders	Very rare (≤1/10,000)	Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical trial and epidemiological data suggest that use of ibuprofen, particularly at high dose (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) (see section 4.4).
Respiratory and thoracic and mediastinal disorders	Very rare (≤1/10,000)	Respiratory reactivity including: asthma, exacerbation of asthma, bronchospasm and dyspnoea.
Gastrointestinal Disorders	Common (≥1/100 to ≤1/10)	Abdominal pain, diarrhoea, dyspepsia, nausea, stomach discomfort and vomiting
	Uncommon (≥1/1,000 to ≤1/100):	Flatulence and constipation
	Uncommon (≥1/1,000 to ≤1/100):	Peptic ulcer, perforation or gastrointestinal haemorrhage, with symptoms of melaena haematemesis sometimes fatal, particularly in the elderly (see section 4.4). Ulcerative stomatitis and exacerbation of ulcerative colitis and Crohn's disease following administration (see section 4.4). Less frequently gastritis has been observed and pancreatitis reported.
Hepatobiliary disorders	Very rare (≤1/10,000)	Abnormal liver function, hepatitis and jaundice. In overdose paracetamol can cause acute hepatic failure, hepatic failure, hepatic necrosis and liver injury (see Section 4.9).

Skin and subcutaneous tissue disorders	Uncommon (≥1/1,000 to ≤1/100)	Rashes of various types including pruritis and urticaria. Angioedema and swelling face.
	Very rare (≤1/10,000)	Hyperhiddrosis, purpura and photosensitivity. Exfoliative dermatoses. Bullous reactions including erythema multiforme, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis.
Renal and urinary disorders	Very rare (≤1/10,000)	Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome, and acute and chronic renal failure.
General disorders and administration site conditions	Very rare (≤1/10,000)	Fatigue and malaise.
Investigations	Common (≥1/100 to ≤1/10)	Alanine aminotransferase increased, gamma-glutamyltransferase increased and liver function tests abnormal with paracetamol. Blood creatinine increased and blood urea increased.
	Uncommon (≥1/1,000 to ≤1/100)	Aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatine phosphokinease increased, blood creatinine increased, haemoglobin decreased and platelet count increased.

4.9 Overdose

Liver damage is possible in adults who have taken 10 g (equivalent to 20 tablets) or more of paracetamol. Ingestion of 5 g (equivalent to 10 tablets) or more of paracetamol may lead to liver damage if the patient has one or more of the risk factors below:

a) Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
b) Regularly consumes alcohol in excess of recommended amounts.
c) Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia

Symptoms

Symptoms of paracetamol overdose in the first 24 hours include pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion as liver function tests become abnormal. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable).

Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol however; the maximum protective effect is obtained up to 8 hours post ingestion. The effectiveness of the antidote declines sharply after this time.

If required the patient should be given intravenous-N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital.

Patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be managed in accordance with established guidelines.

Ibuprofen 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, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. 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 if there is a co-incident of dehydration. 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. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The pharmacological actions of Ibuprofen, Paracetamol & Caffeine differ in their site and mode of action. These complementary modes of action are synergistic which results in greater antinociception and antipyresis than the single actives alone.

Ibuprofen is an NSAID that has demonstrated its efficacy in the common animal experimental inflammation models by inhibition of prostaglandin synthesis. Prostaglandins sensitise nociceptive afferent nerve terminals to mediators such as bradykinin. Ibuprofen therefore elicits an analgesic effect through peripheral inhibition of the cycloxygenase-2 (COX-2) isoenzyme with a subsequent reduction in sensitization of nociceptive nerve terminals. Ibuprofen has also been shown to inhibit induced-leucocyte migration into inflamed areas. Ibuprofen has a pronounced action within the spinal cord due, in part, to the inhibition of COX. Ibuprofen’s antipyretic effects are produced by the central inhibition of prostaglandins in the hypothalamus. Ibuprofen reversibly inhibits platelet aggregation. In humans, ibuprofen reduces inflammatory pain, swellings and fever.

Paracetamol is an antipyretic analgesic. The mechanism of action is probably similar to that of aspirin and dependent on the inhibition of prostaglandin synthesis. The inhibition appears, however, to be on a selective basis. Caffeine is a potent stimulator of the CNS.

5.2 Pharmacokinetic Properties

Ibuprofen is well absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. Ibuprofen diffuses into the synovial fluid. Plasma levels of ibuprofen from this product are detected from 5 minutes with peak plasma concentrations achieved within 1-2 hours after ingestion on an empty stomach. When this product was taken with food peak ibuprofen plasma levels were lower and delayed by a median of 25 minutes, but overall extent of absorption was equivalent.

Ibuprofen is metabolised in the liver to two major metabolites with primary excretion via the kidneys, either as such or as major conjugates, together with a negligible amount of unchanged ibuprofen. Excretion by the kidney is both rapid and complete. The elimination half-life is approximately 2 hours.
In limited studies, ibuprofen appears in the breast milk in very low concentrations.

No significant differences in ibuprofen pharmacokinetic profile are observed in the elderly.
Paracetamol & Caffeine is readily absorbed from the gastrointestinal tract. Plasma protein binding is negligible at usual therapeutic concentrations, although this is dose-dependent. Plasma levels of paracetamol from this product are detected from 5 minutes with peak plasma concentrations occurring at 0.5-0.67 hours after ingestion on an empty stomach. When this product was taken with food peak paracetamol plasma levels were lower and delayed by a median of 55 minutes, but overall extent of absorption was equivalent.

Paracetamol is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates, with about 10% as glutathione conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-life is approximately 3 hours.
A minor hydroxylated metabolite, which is usually produced in very small amounts by mixed function oxidases in the liver and detoxified by conjugation with liver glutathione, may accumulate following paracetamol overdose and cause liver damage.

No significant differences in the paracetamol pharmacokinetic profile are observed in the elderly.
The bioavailability and pharmacokinetic profiles of Caffeine, Ibuprofen and Paracetamol taken as this product are not altered when taken in combination as a single or repeat dose.

This product is formulated using a technology which releases Caffeine, Ibuprofen and Paracetamol simultaneously, so that the active ingredients deliver a combination effect.

5.3. Preclinical safety data

The toxicological safety profile of Caffeine, Ibuprofen and Paracetamol has been established in animal experiments and in humans from extensive clinical experience. There are no new preclinical data of relevance to the prescriber which are additional to the data already presented in this Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose
Maize Starch
Povidone K-30
Methyl Paraben
Propyl Paraben
Tartrazine Supra Colour
Colloidal Anhydrous Silica (Aerosil)
Croscarmellose Sodium
Purified Talc
Polacrillin Potassium (Kyron-T 314)
Sodium Starch Glycolate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Storage below 30^{o}C, Protected from the sunlight.

Keep out of reach of children.

6.5 Nature and contents of container

10 x 1 x 10 Tablets in Alu-Pvc Blister Pack

6.6 Instruction for use and handling

No special requirements

7. APPLICANT

PHARMATRUST LTD.

Scc New Weija Gicel,

Behind Police Station, Accra, Ghana

8. FDA APPLICATION NUMBER

Not Applicable

9. DATE OF REGISTRATION / RENEWAL OF REGISTRATION

FDA/SD.173-121220

10. DATE OF REVISION OF THE TEXT

09/2022