"פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר".
"This leaflet format has been determined by the Ministry of Health and the content thereof has been checked and approved."

NUROFEN® PLUS

TABLETS

Composition

Each tablet contains:

Active Ingredient

Ibuprofen	200 mg
Codeine phosphate hemihydrate (equivalent to codeine 10 mg)	12.8 mg

Other Ingredients

Cellulose, microcrystalline, sodium starch glycollate (*from potato starch*), starch pregelatinised (*from maize, potato, or rice starch*), hypromellose (hydroxypropylmethyl cellulose), titanium dioxide (E 171), talc

Pharmacological Particulars

Pharmacodynamic Properties

Ibuprofen is an analgesic which acts peripherally, inhibiting prostaglandin synthesis and the action of chemical mediators of pain. Codeine is a narcotic analgesic acting on central opiate receptors, although its pharmacological effects are thought to be due largely to its biotransformation to morphine.

The combination of a well tolerated peripheral analgesic with a centrally acting analgesic provides optimum pain relief with a lower potential for producing side-effects.

Pharmacokinetic Properties

The elimination half-life of both ibuprofen and codeine is approximately three hours, and both drugs are given three to fours times daily. The combination of the two drugs is therefore appropriate from a pharmacokinetic viewpoint; the tablet exhibits normal release characteristics for both active substances.

Indications

For the relief of pain in such conditions as: rheumatic and muscular pain, backache, neuralgia, migraine, headache, dental pain, dysmenorrhoea, feverishness, symptoms of colds and influenza.

Contraindications

Known hypersensitivity to the drug or to any ingredient of the preparation.

Patients with a history of, or existing peptic ulceration.

Patients with severe hepatic failure, severe renal failure, severe heart failure.

Previous allergic reaction to any other pain reliever / fever reducer:

Because of potential cross-sensitivity to other NSAIDs (prescription or nonprescription) , ibuprofen should not be used in patients in whom aspirin or other NSAIDs have induced symptoms of asthma, rhinitis, urticaria, nasal polyps, angioedema, bronchospasm and other symptoms of allergic reactions (anaphylactoid reactions have occurred in such patients).

Patients who recently had or are about to have heart surgery (see also "Precautions").

Hypersensitivity to codeine, respiratory depression, chronic constipation.

Warnings

Long- term use of ibuprofen may increase the risk of heart attack or stroke.

Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin.

This product contains a nonsteroidal anti- inflammatory drug (NSAID), which may cause stomach bleeding. The chance is higher if the patient is: over 60, has had stomach ulcers or bleeding problems, takes a blood thinning (anticoagulant) or steroid drug, takes other drugs containing an NSAID (aspirin, ibuprofen , naproxen or others), has 3 or more alcoholic drinks every day while using this product. Longer duration of use and higher dosages are also risk factors.

Ibuprofen should be administered under close supervision to patients with a history of upper gastrointestinal tract disease. If symptoms persist, worsen, or new symptoms develop, the physician should be referred to.

Nurofen Plus tablets should be used with caution in those with hypotension and/ or hypothyroidism. The tablets should be used with caution in patients with raised intracranial pressure or head injury.

Use in Pregnancy

Administration of ibuprofen is not recommended during pregnancy.

The onset of labor may be delayed and duration of labor increased, therefore it is recommended not to use ibuprofen during the last 3 months of pregnancy.

Based on animal studies and limited clinical experience there is no evidence to suggest foetal abnormalities associated with the use of codeine. However, the product should be avoided during pregnancy.

Use in Breastfeeding

Ibuprofen appears in breast milk in very low concentrations and is unlikely to affect the breastfed infant adversely.

Codeine is excreted in breast milk.

Use in Pediatrics

This product is not to be used in children under 12 years of age.

Adverse Reactions

Adverse Reactions Attributed to Ibuprofen

Gastrointestinal

Epigastric pain, heartburn, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of gastrointestinal tract, dyspepsia, gastrointestinal bleeding, peptic ulceration,.

Central Nervous System

Dizziness, severe headache, nervousness, convulsions, pain in the spinal column.

Dermatological

Rash (including maculopapular type), pruritus, photosensitivity, skin peeling.

Rarely exfoliative dermatitis and epidermal necrolysis have been reported with ibuprofen.

Special Senses

Hearing disturbance.

Metabolic/Endocrine

Decreased appetite.

Cardiovascular

Edema, fluid retention (generally responds to drug discontinuation, see Precautions).

Hematological

Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia, thrombocytopenia, decreased hemoglobin and hematocrit.

Allergic

Fever.

Bronchospasm may be precipitated in patients with a history of aspirin-sensitive asthma

Other Hypersensitivity Reactions:

Rarely hypersensitivity reactions with cutaneous eruptions, urticaria and pruritus, as well as attacks of asthma, with or without drop in blood pressure, have been observed. In single cases, severe hypersensitivity reactions, manifesting as facial edema, swelling of the tongue, swelling of the larynx, dyspnea, tachycardia, hypotension or severe shock have been reported. If these symptoms occur, immediate medical attention is necessary.

In single cases, serious forms of skin reactions such as erythema multiforme can occur.

In patients with existing auto-immune disorders (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.

Other

Stiffness, sudden decrease in the amount of urine, black stools.

Renal papillary necrosis which can lead to renal failure.

Adverse Reactions Attributed to Codeine

Side effects to codeine include constipation, respiratory depression, cough suppression, nausea and drowsiness

Precautions

Note

Patients sensitive to one of the non-steroidal anti-inflammatory agents (NSAIDs) may be sensitive to any of the other NSAIDs also.

Blurred and/or diminished vision, scotomata, and changes in color vision have been reported. If a patient develops such complaints while receiving ibuprofen, the drug should be discontinued and the patient should have an ophthalmological examination which includes central visual fields and color vision testing.

As with other NSAIDs, patients should be cautioned about engaging in activities requiring mental alertness and motor coordination, such as driving a car.

Physicians should be consulted if patients taking ibuprofen exhibit signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

Fluid retention and edema have been reported in association with ibuprofen. Therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored, and a reduction in dosage should be anticipated to avoid drug accumulation.

Ibuprofen should be used with caution in individuals with intrinsic coagulation defects, and those on anticoagulant therapy.

Caution should be exercised when this product is administered to asthma sufferers since bronchospasm may be precipitated in patients suffering from, or with a previous history of bronchial asthma or allergic disease.

The elderly are at increased risk of the consequence of adverse reactions.

Undesirable effects may be minimised by using the minimum effective dose for the shortest possible duration.

Monitoring of blood urea nitrogen (BUN), serum creatinine concentrations and/or serum potassium concentrations may be required at periodic intervals during therapy, especially in patients with documented hepatic or renal function impairment.
The same monitoring may also be required in patients known or suspected to be at risk for renal function impairment, patients taking diuretics concurrently, and in patients in whom signs of possible renal toxicity occur, such as substantial increases in blood pressure, fluid retention, or rapid weight gain.

In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy reduced slowly, rather than discontinued abruptly, when ibuprofen is added to the treatment regimen.

As with other non-steroidal anti-inflammatory agents, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, remain essentially unchanged, or be transient with continued therapy.

Because serious gastrointestinal tract ulcerations and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulcerations and bleeding and should inform them (in case of children, the child's parent/guardian) of importance of this follow-up.

Patients with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with ibuprofen. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other non-steroidal anti-inflammatory agents. Although such reactions are rare, if abnormal liver tests persist or worsen, or clinical signs and symptoms consistent with liver disease develop, or systemic manifestations occur (e.g., eosinophilia, rash, etc.), ibuprofen should be discontinued.

In cross-study comparisons with doses ranging from 1200-3200 mg daily for several weeks, a slight dose-response decrease in hemoglobin/hematocrit was noted.

Aseptic meningitis with fever and coma has been observed on rare occasions in patients on ibuprofen therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease. If signs or symptoms of meningitis develop in a patient on ibuprofen, the possibility of its being related to ibuprofen should be considered.

There is some 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.

Patients Who Require Surgery (Including Dental Surgery)

Caution is recommended in patients who require surgery. Most of the Nonsteroidal anti-inflammatory agents inhibit platelet aggregation and may prolong bleeding time, which may increase intra-and postoperative bleeding. Consideration should therefore be given to discontinuing NSAIDs treatment for an appropriate length of time prior to elective surgery, depending on the potency and duration of effect of the individual agent on platelet aggregability.

In case of patients requiring dental surgery, nonsteroidal anti-inflammatory agents may cause soreness, irritation, or ulceration of the oral mucosa. Most of the nonsteroidal anti-inflammatory agents may rarely cause leukopenia and/or thrombocytopenia, which may result in an increased incidence of microbial infection, delayed healing, and gingival bleeding. If leukopenia or thrombocytopenia occurs, dental work should be deferred until blood counts return to normal, and patients should be instructed in proper oral hygiene.

Drug Interactions

Ibuprofen/Coumarin-Type Anticoagulants: Because bleeding has been reported when ibuprofen and other non-steroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants, physicians should exercise caution when administering ibuprofen to patients on anticoagulants.

Ibuprofen/Aspirin/Non-Steroidal Anti-Inflammatory Agents (NSAIDs): Animal studies have demonstrated that aspirin administered with NSAIDs causes a decrease in blood levels and activity of non-aspirin drugs. Since concomitant use offers no therapeutic advantage, such combinations should be avoided.

Ibuprofen/Methotrexate*:* Animal studies indicate that ibuprofen, as well as other NSAIDs, may enhance the toxicity of methotrexate. Caution should be used if ibuprofen is administered concomitantly with methotrexate.

Ibuprofen/Beta-Blockers**:** As with other nonsteroidal anti-inflammatory agents , the antihypertensive effect of beta-blockers may be reduced.

Ibuprofen/Furosemide/Thiazides*:* Clinical studies, as well as random observations, have shown that ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. During concomitant therapy with ibuprofen, patients should be observed closely for signs of renal failure, as well as to assure diuretic efficacy.

Ibuprofen/Lithium: Ibuprofen may produce an elevation of plasma lithium levels and a reduction in renal lithium clearance. Therefore, when ibuprofen and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Ibuprofen/Alcohol: Concomitant use of non-steroidal anti-inflammatory agents with alcohol may increase the risk of gastrointestinal side effects, including ulceration or hemorrhage.

Ibuprofen/Probenecid: Probenecid may decrease excretion and increase the serum concentration of NSAIDs, possibly enhancing effectiveness and/or increasing the potential for toxicity of these agents. A decrease in dosage of the NSAIDs may be considered necessary.

Ibuprofen/Zidovudine: There is evidence of prolonged bleeding time in patients receiving concurrent treatment with zidovudine and ibuprofen.

Codeine/Monoamine Oxidase (MAO) Inhibitors: Codeine interacts with monoamine oxidase inhibitors.

Dosage and Administration

Notes

This product should be taken with or after food.

The tablets should not to be used for more than 10 days for the treatment of pain, or for more than 3 days for the treatment of fever, unless instructed by the physician.

The smallest effective dose should be used.

In primary dysmenorrhea, Nurofen Plus Tablets should be taken immediately following the onset of pain.

Recommended dosage:

Adults:

One or two tablets every four to six hours.

Children under 12 years:

Not recommended.

Elderly:

No special dosage modifications are required for elderly patients, unless renal or hepatic function is impaired, in which case dosage should be assessed individually.

Do not take more than 6 tablets in 24 hours.

Overdosage

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.

For Ibuprofen

Manifestations

Symptoms include nausea, headache, vomiting, dizziness, drowsiness, nystagmus, blurred vision, tinnitus, and, rarely, hypotension, metabolic acidosis, renal failure, and, loss of consciousness. Large overdoses are generally well tolerated when no other drugs are involved.

Treatment

No special antidote is available.

Patients should be treated symptomatically as required. Use supportive care where appropriate. Within one hour of ingestion, activated charcoal or gastric lavage followed by activated charcoal if the dose is greater than 400 mg/kg, can be used.

For Codeine

Manifestations

Nausea and vomiting are prominent features of codeine overdose. Respiratory depression, excitability, convulsions, hypotension and loss of consciousness may occur with large codeine overdose.

Treatment

The stomach should be emptied. If severe CNS depression has occurred, artificial respiration, oxygen and parenteral naloxone may be needed. Imbalance in electrolyte levels should be considered

Storage

Store in a dry place below 25oC.

Presentation

Bottles of 100 and 200 tablets.
Blisters of 6, 12, 24, 60, and 72 tablets.

Manufacturer

Boots Healthcare International
Nottingham, England

Importer

Abic Marketing Ltd
P.O.Box 8077, Netanya.