

NUROFEN FOR CHILDREN ORANGE SUGAR FREE SUSPENSION 200MG/5ML

Ibuprofen 200mg/5ml

DESCRIPTION

An off-white, syrupy suspension with characteristic orange odour & taste.

PHARMACOLOGY

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) that has demonstrated its efficacy in the common animal experimental inflammation models by inhibition of prostaglandin synthesis. In humans, ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

The clinical efficiency of ibuprofen has been demonstrated in the treatment of mild to moderate pain such as pain through toothache, headache and in symptomatic treatment of fever.

The analgesic dose for children is 7 to 10 mg/kg per dose with a maximum of 30 mg/kg/day. Nurofen for Children gets to work in 15 minutes and decreases fever in children for up to 8 hours.

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are used concomitantly. In one study, when a single dose of ibuprofen 400 mg was taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81 mg), a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusion can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

Pharmacokinetics:

No special studies on pharmacokinetics have been carried out in children. Literature data confirm that the absorption, metabolism and elimination of ibuprofen in children proceed in the same way as in adults.

After oral administration ibuprofen is partly absorbed in the stomach and afterwards completely in the small intestine. After hepatic metabolism (hydroxylation, carboxylation, conjugation) the pharmacologically inactive metabolites are eliminated completely, mainly renally (90 %), as well as via the biliary route. The elimination half-life for healthy persons as well as for patients suffering from hepatic or renal diseases is 1.8 to 3.5 hours. Plasma protein binding is about 99 %.

Renal impairment

Since ibuprofen and its metabolites are primarily eliminated by the kidneys, patients with varying degrees of renal impairment may display altered pharmacokinetics of the drug. For patients with renal impairment decreased protein binding, increased plasma levels for total ibuprofen and unbound (S)- ibuprofen, higher AUC values for (S)- ibuprofen and increased enantiomeric AUC (S/R) ratios as compared with healthy controls have been reported. In end-stage renal disease patients receiving dialysis the mean free fraction of ibuprofen was about 3% compared with about 1% in healthy volunteers. Severe impairment of renal function may result in accumulation of ibuprofen metabolites. The significance of this effect is unknown. The metabolites can be removed by haemodialysis (see also section contraindications)

Hepatic impairment

Alcoholic liver disease with mild to moderate hepatic impairment did not result in substantially altered pharmacokinetic parameters. Hepatic disease can alter the disposition kinetics of ibuprofen. In cirrhotic patients with moderate hepatic impairment (Child Pugh's score 6-10) an average 2-fold prolongation of the half-life was observed and the enantiomeric AUC ratio (S/R) was significantly lower compared to healthy controls suggesting an impairment of metabolic inversion of (R)- ibuprofen to the active (S)- enantiomer (see also section contraindications)

INDICATIONS

For the short-term symptomatic treatment of mild to moderate pain.

For the short-term symptomatic treatment of fever.

DOSAGE AND ADMINISTRATION

For pain and fever: The daily dosage of Nurofen for Children is 20-30 mg/kg bodyweight in divided doses. Using the measuring device provided this can be achieved as follows:

Child's age (Weight)	Quantity and method of administration	Frequency in 24 hours
20-29kg (6-9 years)	1 x 200mg/5ml (using the correct end of the spoon once)	3 times
30-40kg (10-12 years)	1 x 300mg/7.5ml (using the spoon twice (5ml & 2.5ml))	3 times

Doses should be given approximately every 6 to 8 hours.

For patients with sensitive stomachs it is recommended that Nurofen for children is taken during a meal

Not intended for children under 6 years of age or under 20kg.

For oral use.

For short-term use only.

If symptoms worsen medical advice should be sought.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section Warning and Precautions)

Special patient groups

Renal insufficiency: (see section Pharmacokinetics):

No dose reduction is required in patients with mild to moderate impairment to renal function (patients with severe renal insufficiency, see section contraindications).

Hepatic insufficiency (see section Pharmacokinetics):

No dose reduction is required in patients with mild to moderate impairment to hepatic function (patients with severe hepatic dysfunction, see section contraindications).

CONTRAINDICATIONS

Hypersensitivity to ibuprofen or other non-steroidal anti-inflammatory drugs (NSAIDs) or to any of the excipients.

Patients with a history of bronchospasm, asthma, rhinitis or urticaria associated with the intake of acetylsalicylic acid or other non-steroidal anti-inflammatory medicinal products.

Patients with a history of gastrointestinal bleeding or perforation, related to previous NSAID therapy.

Patients with active, or a history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

Cerebrovascular or other active bleeding.

Patients with severe hepatic failure, severe renal failure or severe heart failure (see section Warning and Precautions).

Coagulation disorders (ibuprofen may increase bleeding time).

Unclearified blood-formation disturbances such as thrombocytopenia.

Last trimester of pregnancy (see section Pregnancy and Lactation).

INTERACTIONS WITH OTHER MEDICAMENTS

Monitoring of clinical and biological parameters should be considered in patients taking ibuprofen concomitantly with the medicinal products listed below.

Concomitant use with the following medicinal products is not recommended:

Acetylsalicylic acid or other NSAIDs and glucocorticoids. These may increase the risk of adverse reactions in the gastro-intestinal tract.

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on 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 (see section Pharmacodynamics).

Precautions are required during concomitant use with the following medicinal products:

Diuretics, ACE inhibitors, beta-receptor blocking medicines and angiotensin-II antagonists:

NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor, betareceptor blocking medicine or angiotensin-II antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

The concomitant administration of Nurofen for Children and potassium-sparing diuretics may lead to hyperkalaemia.

Digoxin, phenytoin, lithium: The concomitant use of Nurofen for Children with digoxin, phenytoin or lithium preparations may increase serum levels of these medicinal products. A check of serum-lithium, serum-digoxin and serum-phenytoin levels is not as a rule required on correct use (maximum over 3 to 4 days).

Methotrexate: There is evidence for the potential increase in plasma levels of methotrexate. NSAIDs inhibit the tubular secretion of methotrexate and decreased clearance of methotrexate may occur. For high-dose methotrexate treatment, ibuprofen (NSAIDs) should be avoided. The risk of an interaction between NSAIDs and methotrexate must also be considered with low dose methotrexate treatment, especially in patients with renal impairment. When methotrexate and NSAIDs are combined, the renal function should be monitored. Caution is advised if both NSAIDs and methotrexate are administered within 24 hours, as the plasma levels of methotrexate may increase and result in increased toxicity.

Tacrolimus: The risk of nephrotoxicity is increased when both medicinal products are given concomitantly.

Ciclosporin: There is limited evidence of a possible interaction leading to an increased risk of nephrotoxicity.

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (See section Warning and Precautions).

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section Warning and Precautions).

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section Warning and Precautions).

Sulphonylureas: Clinical investigations have shown interactions between NSAIDs and antidiabetics (sulphonylureas). Although interactions between ibuprofen and sulphonylureas have not been described to date, a check of blood-glucose values is recommended as a precaution on concomitant intake.

Zidovudine: There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Probenecid and sulfinpyrazone: Medicinal products that contain probenecid or sulfinpyrazone may delay the excretion of ibuprofen.

Baclofen: Baclofen toxicity may develop after starting ibuprofen.

Ritonavir: Ritonavir may increase the plasma concentrations of NSAIDs.

Aminoglycosides: NSAIDs may decrease the excretion of aminoglycosides.

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.

In a study with voriconazole and fluconazole (CYP2C9 inhibitors) an increased S (+) ibuprofen exposure by approximately 80-100% has been shown. Reduction of ibuprofen dose should be considered when potent CYP2C9 inhibitors are administered concomitantly, particularly when high-dose ibuprofen is administered with either voriconazole or fluconazole

Captopril: Experimental studies indicate that ibuprofen inhibits the sodium excretion effect of captopril.

Cholestyramine: At concomitant administration of ibuprofen and cholestyramine the absorption of ibuprofen is delayed and decreased (25%). The medicinal products should be administered with a few hours interval.

PRECAUTIONS / WARNINGS

Caution is required in patients with:

- Systemic lupus erythematosus as well as those with mixed connective tissue disease - increased risk of aseptic meningitis (see Section Side Effects)
- A history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy (see Section Contraindication and Section Side Effects)
- Renal impairment as renal function may further deteriorate (see Section Contraindication and Section Side Effects)
- Hepatic dysfunction (see Section Contraindication and Section Side Effects)
- Directly after major surgery

Bronchospasm may be precipitated in patients suffering from, or with a history of, bronchial asthma or allergic disease.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see gastrointestinal and cardiovascular risks).

Use with concomitant NSAIDs including cyclo-oxygenase-2 selective inhibitors should be avoided.

Elderly

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section Recommended Dose)

Gastrointestinal safety

Gastrointestinal bleeding, ulceration or perforation, which can be fatal, have been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events.

The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (See Section Contraindication) and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (eg 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 Interactions with other medicaments)

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stage 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, or anti-platelet agents such as acetylsalicylic acid (See Section Interactions with other medicaments).

When gastrointestinal bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section Side Effects)

Skin reactions

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 Side Effects). 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. Nurofen for Children should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissues infectious complications.

To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of ibuprofen in case of varicella.

Cardiovascular and cerebrovascular effects

Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID 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.

Other notes:

Severe acute hypersensitivity reactions (for example anaphylactic shock) are observed very rarely. At the first signs of a hypersensitivity reaction after taking/administering Nurofen for Children therapy must be stopped. Medically required measures, in line with the symptoms, must be initiated by specialist personnel.

Ibuprofen, the active substance of Nurofen for Children, may temporarily inhibit the blood-platelet function (thrombocyte aggregation). Patients with coagulation disturbances should therefore be monitored carefully.

Results of experimental investigations indicate an attenuation of the thrombocyte aggregation-inhibiting effect of acetylsalicylic acid on concomitant administration of ibuprofen. This interaction could reduce the desired protective cardiovascular effect of ASA. Ibuprofen should therefore only be used with particular caution in patients who are receiving ASA to inhibit thrombocyte aggregation (see section Interactions with other medicaments). In prolonged administration of Nurofen for Children, regular checking of the liver values, the kidney function, as well as of the blood count, is required.

On prolonged use of painkillers, headache may occur that must not be treated with increased doses of the medicinal product.

In general terms, the habitual intake of painkillers, particularly on combination of several pain-relieving active substances, may lead to permanent renal damage with the risk of renal failure (analgesic nephropathy). This risk may be increased under physical strain associated with loss of salt and dehydration therefore it should be avoided.

Adult patients taking non-steroidal anti-inflammatory painkillers, or aspirin with a daily dose above 75mg should avoid taking this medicine.

There is a risk of renal insufficiency in dehydrated children.

NSAIDs may mask symptoms of infection and fever

This product contains maltitol liquid.

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

This medicinal product contains wheat starch.

Wheat starch may contain gluten, but only in trace amounts, and is therefore considered safe for people with coeliac disease. (Gluten in wheat starch is limited by the test for total protein described in the Ph.Eur. monograph).

Risk of GI Ulceration, Bleeding and Perforation with NSAID

Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious GI events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking, and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.

PREGNANCY AND LACTATION

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The risk is believed to increase with dose and duration of therapy. 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.

During the first and second trimester of pregnancy, ibuprofen should not be given unless clearly necessary. If ibuprofen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all 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

the mother and the neonate, at the end of pregnancy, 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.

Consequently, ibuprofen is contraindicated during the third trimester of pregnancy.

Lactation

Only small amounts of ibuprofen and its decomposition products pass into the breast milk. As no harmful effects to infants are known to date, it is not usually necessary to interrupt breast feeding during short-term use of ibuprofen at the recommended doses.

Female fertility

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

ADVERSE EFFECTS

The following frequencies are taken as a basis when evaluating side effects:

Very common: 1/10	Common: $\geq 1/100$ to $< 1/10$
Uncommon: $\geq 1/1,000$ to $< 1/100$	Rare: $\geq 1/10,000$ to $< 1/1,000$
Very rare: $< 1/10,000$,	Not known: cannot be estimated from the available data

The list of the following undesirable effects comprises all undesirable effects that have become known under treatment with ibuprofen, also those under high-dose long-term therapy in rheumatism patients. The stated frequencies, which extend beyond very rare reports, refer to the short-term use of daily doses up to a maximum of 1200 mg ibuprofen for oral dosage forms and a maximum of 1800 mg for suppositories (= 60 ml oral suspension of Nurofen for Children maximum daily dose for adults and children older than 12 years).

Infections and infestations

Very rarely, exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of non-steroidal anti-inflammatory drugs has been described. This is possibly associated with the mechanism of action of the non-steroidal anti-inflammatory drugs.

If signs of an infection occur or get worse during use of Nurofen for Children, the patient is therefore recommended to go to a doctor without delay. It is to be investigated whether there is an indication for an anti-infective/antibiotic therapy.

Very rarely, the symptoms of aseptic meningitis with neck stiffness, headache, nausea, vomiting, fever or consciousness clouding have been observed under ibuprofen. Patients with autoimmune disorders (SLE, mixed connective-tissue disease) appear to be predisposed.

Blood and lymphatic system disorders

Very rare: Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, nose and skin bleeding.

Immune system disorders

Uncommon: Hypersensitivity reactions with skin rashes and itching, as well as asthma attacks (possibly with drop in blood pressure).

The patient is to be instructed to inform a doctor at once and no longer to take Nurofen for Children in this case.

Very rare: Severe general hypersensitivity reactions. They may present as face oedema, swelling of the tongue, swelling of the internal larynx with constriction of the airways, respiratory distress, racing heart, drop in blood pressure up to life-threatening shock.

If one of these symptoms occurs, which can happen even on first use, the immediate assistance of a doctor is required.

Psychiatric disorders

Very rare: Psychotic reactions, depression.

Nervous system disorders

Uncommon: Central nervous disturbances such as headache, dizziness, sleeplessness, agitation, irritability or tiredness.

Eye disorders

Uncommon: Visual disturbances.

Ear and labyrinth disorders

Rare: Tinnitus.

Cardiac disorders

Very rare: Palpitations, heart failure, myocardial infarction.

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical trial and epidemiological data suggest that the use of ibuprofen (particularly at high doses 2400mg daily) and in long-term treatment may be associated with small increased risk of arterial thrombotic events

(for example myocardial infarction or stroke)(see section Warning and Precautions)

Vascular disorders

Very rare: Arterial hypertension.

Gastrointestinal

The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section Warning and Precautions). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (See section Warning and Precautions have been reported following administration. Less frequently, gastritis has been observed.

Common: Gastro-intestinal complaints such as pyrosis, abdominal pain, nausea, vomiting, flatulence, diarrhea, constipation and slight gastro-intestinal blood losses that may cause anaemia in exceptional cases.

Uncommon: Gastrointestinal ulcers, potentially with bleeding and perforation. Ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section Warning and Precautions), gastritis.

Very rare: Oesophagitis, pancreatitis, formation of intestinal, diaphragm-like strictures.

The patient is to be instructed to withdraw the medicinal product and to go to a doctor immediately if severe pain in the upper abdomen or melaena or haematemesis occurs.

Hepatobiliary disorders

Very rare: Hepatic dysfunction, hepatic damage, particularly in long-term therapy, hepatic failure, acute hepatitis.

Skin and subcutaneous tissue disorders

Very rare: Severe forms of skin reactions such as erythema multiforme can occur. Bullous reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis.

Exceptionally, occurrence of serious cutaneous and soft tissues infectious complications during varicella.

Renal and urinary disorders

Very rare: Decrease of urea excretion, oedema can occur, particularly in patients with arterial hypertension. Also, renal insufficiency, nephritic syndrome, interstitial nephritis that may be accompanied by acute renal failure is possible.

Papillary necrosis especially in long term use.

Increased serum urea concentrations.

OVERDOSAGE

Symptoms of Overdose

The symptoms of overdose can include nausea, vomiting, abdominal pain, headache, dizziness, drowsiness, nystagmus, blurred vision, tinnitus and rarely hypotension, metabolic acidosis, renal failure and loss of consciousness.

Therapeutic Measure in Overdose

No special antidote is available.

Patients should be treated symptomatically as required. Supportive care where appropriate.

STORAGE CONDITIONS

Do not store above 30°C.

SHELF LIFE

24 months

PACKAGING & PACK SIZE

The product is supplied in amber polyethylene terephthalate (PET) bottles. It is available in 100ml bottle.

Manufactured by:

Reckitt Benckiser Healthcare (UK) Limited

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