# Nurofen for Children Forte Strawberry 200mg/5ml suspension
# Nurofen for Children Forte Orange 200mg/5ml suspension

Prescribing Information

## 1. NAME OF THE MEDICINAL PRODUCT

Nurofen for Children Forte Strawberry 200mg/5ml suspension
Nurofen for Children Forte Orange 200mg/5ml suspension

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral suspension contains 40 mg ibuprofen.

Excipients:
Nurofen for Children Forte Orange 200mg/5ml suspension
Maltitol liquid 442 mg/ml
Wheat starch 3.1mg/ml

Nurofen for Children Forte Strawberry 200mg/5ml suspension
Maltitol liquid 442 mg/ml
Propylene Glycol 3.3 mg/ml

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Oral suspension.
Nurofen for Children Forte Strawberry 200mg/5ml suspension:
An off-white, syrupy suspension with characteristic strawberry odor.

Nurofen for Children Forte Orange 200mg/5ml suspension:
An off-white, syrupy suspension with characteristic orange odor.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

For the reduction of fever and relief of mild to moderate pain. For infants and children aged 3 months to 12 years (i.e. weighing about 40 kg).

### 4.2 Posology and method of administration

**Posology**
The lowest effective dose should be used for the shortest duration necessary to relieve symptoms (see section 4.4).

For pain and fever: The daily dosage of Nurofen for Children Forte aged 6 months to 12 years old is 5 to 10 mg/kg ORALLY every 6 to 8 hours as needed MAX 4 doses/day. Infants and children aged 3 -6 months: dosage according to physician’s prescription only.

Children with identical ages can have significantly different weights. Therefore, try to obtain the weight of the child and determine the dosage by weight. Only if you cannot find the child's weight determine the dosage according to age.

Using the syringe device provided, this can be achieved as follows:

| Weight | Age | Dosage | Num. of Times in 24 hours |
|---|---|---|---|
| Under 5 kg | 3-6 months | According to physician's prescription only | |
| 5 - 5.4 kg | | 1 ml | 3-4 times |
| 5.5-8.1 kg | 6-11 months | 1.25 ml | |
| 8.2-10.9 kg | 12-23 months | 1.75 ml | |
| 11 - 15 Kg | 2- 3 years | 2.5 ml | |
| 16 - 21 kg | 4-5 years | 3.75 ml | |
| 22 – 26 kg | 6-8 years | 5 ml | |
| 27- 32 kg | 9-10 years | 6.25 ml | |
| 33 – 43 kg | 11-12 years | 7.5 ml | |

Doses should be given approximately every 6 to 8 hours, (or with a minimum of 4 hours between each dose if required).
Not suitable for children under 3 months of age unless advised by your doctor.
For short term use only.
If the child's (aged over 6 months) symptoms persist for more than 3 days, consult your doctor.
For children under 6 months, medical advice should be sought after 24 hours use (3 doses) if the symptoms persist.

**Special patient groups**

Renal insufficiency: (see section 5.2)
No dose reduction is required in patients with mild to moderate impairment to renal function (patients with severe renal insufficiency, see section 4.3).

Hepatic insufficiency (see section 5.2):
No dose reduction is required in patients with mild to moderate impairment to hepatic function (patients with severe hepatic dysfunction, see section 4.3).

**Method of administration**
For oral administration.

For patients with sensitive stomachs the product can be taken with or after food.

**4.3 Contraindications**

- In patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- In patients who have previously shown hypersensitivity reactions (e.g bronchospasm, asthma, rhinitis, angioedema or urticaria) associated with acetylsalicylic acid, ibuprofen or other non-steroidal anti-inflammatory medicinal products.
- In patients with a history of gastrointestinal bleeding or perforation, related to previous NSAID therapy.
- In patients with active, or a history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- In patients with cerebrovascular or other active bleeding.
- In patients with severe hepatic failure or severe renal failure
- In patients with severe heart failure (NYHA IV)

- In patients with unclarified blood-formation disturbances.
- During the last trimester of pregnancy (see section 4.6).
- In patients with severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake).

**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.

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal. The elderly are at increased risk of the consequences of adverse reactions.

Caution is required in patients with:
- Systemic lupus erythematosus as well as those with mixed connective tissue disease, due to increased risk of aseptic meningitis (see Section 4.8)
- Congenital disorder of porphyrin metabolism (e.g. acute intermittent porphyria)
- Gastrointestinal disorders and chronic inflammatory intestinal disease (ulcerative colitis, Crohn's disease) (see section 4.8)
- A history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy (see Section 4.3 and Section 4.8)
- Renal impairment as renal function may further deteriorate (see Section 4.3 and Section 4.8)
- Hepatic dysfunction (see Section 4.3 and Section 4.8)
- Directly after major surgery
- Hay fever, nasal polyps or chronic obstructive respiratory disorders as an increased risk for them of allergic reactions occurring. These may be present as asthma attacks (so-called analgesic asthma), Quincke's oedema or urticaria.
- In patients who have already reacted allergically to other substances, as an increased risk of hypersensitivity reactions occurring also exists for them on use of this product.

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

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

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 4.3) and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective medicinal products (eg Misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients

requiring concomitant low dose acetylsalicylic acid, or other medicinal products likely to increase gastrointestinal risk (see below and 4.5)
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 medicinal products which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet medicinal products such as acetylsalicylic acid (See Section 4.5).
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 4.8)

Severe skin reactions:
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported 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. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. Nurofen for Children 200 mg/5 ml Orange should be discontinued at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.
Masking of symptoms of underlying infections :
This medicine 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 Nurofen for Children Forte Strawberry/Orange 200mg/5ml suspension 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.
Exceptionally, varicella can be at the origin of serious cutaneous and soft tissues infectious complications. Thus, it is advisable to avoid use of ibuprofen in case of varicella.

Cardiovascular and cerebrovascular effects
Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) 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/day) is associated with an increased risk of arterial thrombotic events.
Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) should be avoided.
Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

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 200 mg/5 ml Orange therapy must be

stopped. Medically required measures, in line with the symptoms, must be initiated by specialist personnel.
Ibuprofen may temporarily inhibit the blood-platelet function (thrombocyte aggregation). Patients with coagulation disturbances should therefore be monitored carefully.
In prolonged administration of Nurofen for Children 200 mg/5 ml Orange, regular checking of the liver values, the kidney function, as well as of the blood count is required.
Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of medication overuse headache (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

Through concomitant consumption of alcohol, active substance-related undesirable effects, particularly those that concern the gastrointestinal tract or the central nervous system, may be increased on use of NSAIDs.

Renal:
In general the habitual use of analgesics, especially the combination of different analgesics, can lead to lasting renal lesions with the risk of renal failure (analgesic nephropathy).
There is a risk of renal impairment in dehydrated children.

Excipient warnings:
**Nurofen for Children Forte Strawberry 200mg/5ml suspension**
This medicinal product contains maltitol liquid and Propylene Glycol.

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

This medicinal product contains 1.87 mg sodium per 1 ml suspension. To be taken into consideration by patients on a controlled sodium diet.

**Nurofen for Children Forte Orange 200mg/5ml suspension**
This medicinal product contains maltitol liquid.

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

This medicinal product contains 1.87 mg sodium per 1 ml suspension. To be taken into consideration by patients on a controlled sodium diet.

Wheat starch in this medicine contains only very low levels of gluten, regarded as gluten-free, and is very unlikely to cause problems if you have coeliac disease.
One ml contains no more than 0.06 micrograms of gluten.
If you have wheat allergy (different from coeliac disease) you should not take this medicine.

**4.5 Interaction with other medicinal products and other forms of interaction**

<u>Ibuprofen should be avoided in combination with:</u>

Other NSAIDs including cyclooxygenase-2 selective inhibitors: concomitant use of two or more NSAIDs should be avoided as this may increase the risk of adverse effects (see section 4.4).

Acetylsalicylic acid:
Concomitant administration of ibuprofen and acetylsalicylic acid is not generally recommended because of the potential of increased adverse effects.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

Ibuprofen should be used with caution in combination with:
Antihypertensives (ACE inhibitors, betareceptor blocking medicinal products and angiotensin-II antagonists) and diuretics:
NSAIDs may reduce the effect of these medicinal products. 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 medicinal product or angiotensin-II antagonists and medicinal product 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. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Cardiac glycosides: e.g. Digoxin: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels. The concomitant use of ibuprofen with medicinal products containing digoxin may increase serum level of digoxin. A check of serum digoxin is not as a rule required on correct use (maximum over 3 days).

Lithium: There is evidence for the potential increase in plasma levels of lithium. A check of serum lithium is not as a rule required on correct use (maximum over 3 days).

Potassium sparing diuretics: The concomitant administration of ibuprofen and potassium-sparing diuretics may lead to hyperkalaemia. (check of serum potassium is recommended).

Phenytoin:
The concomitant use of ibuprofen with phenytoin preparations may increase serum level of phenytoin. A check of serum-phenytoin levels is not as a rule required on correct use (maximum over 3 days).

Methotrexate. There is evidence for the potential increase in plasma levels of methotrexate. The administration of ibuprofen within 24 hours before or after administration of methotrexate may lead to elevated concentrations of methotrexate and an increase in its toxic effect.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Ciclosporin: Increased risk of nephrotoxicity.

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (See section 4.4).

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4).

Anti-platelet medicinal products and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).

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.

CYP2C9 inhibitors: Concomitant administration of Ibuprofen with CYP2C9 inhibitors may increase the exposure to ibuprofen (CYP2C9 substrate). 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.

**4.6 Fertility, 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. 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.

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.

Rarely, taking NSAIDs after the 20th week of pregnancy may cause impaired renal function of the fetus, which may cause low levels of amniotic fluid (oligohydramnios).

The effects were observed after days to weeks of treatment. However, in rare cases, low levels of amniotic fluid were observed already after 48 hours of taking NSAIDs. In most cases, oligohydramnios passed with the treatment discontinuation.

Using NSAIDs after the 20th week of pregnancy should be limited. If it was decided that the benefit outweighs the risk for the fetus and the treatment with the medicine is essential after the 20th week of pregnancy, the lowest effective dose should be used for the shortest possible period.

Referring the patient to ultrasound scan should be considered, in order to estimate the amount of amniotic fluid when the treatment with therapeutic dosage of these medicines exceeding 5 days and stopping the treatment if low levels of amniotic fluid is detected.

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.

Breast-feeding

Ibuprofen and its metabolites can pass in low concentrations into the breast milk. No harmful effects to infants are known to date, so for short-term treatment with the recommended dose for pain and fever interruption of breast feeding would not generally be necessary.

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 of treatment.

**4.7 Effects on ability to drive and use machines**
For short-term use this medicinal product, has no or negligible influence on the ability to drive and use machines.

**4.8 Undesirable effects**
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.

With the following adverse drug reactions, it must be accounted for that they are predominantly dose-dependent and vary inter-individually.

Adverse events which have been associated with Ibuprofen are given below. Listed by system organ class and frequency. Frequencies are defined as:

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

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

The adverse events observed most often are gastrointestinal in nature. Adverse events are mostly dose-dependent in particular the risk of occurrence of gastrointestinal bleeding which is dependent on the dose range and duration of treatment. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (See section 4.4) have been reported following administration. Less frequently, gastritis has been observed.

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

Clinical studies suggest that use of ibuprofen, particularly at high dose (2400 mg daily), may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Exacerbation of infection-related inflammations (e.g development of necrotizing fasciitis) coinciding with the use of nonsteroidal anti-inflammatory drugs has been described. This is possibly associated with the mechanism of action of the nonsteroidal anti-inflammatory drugs.

If signs of an infection occur or get worse during use of Nurofen for Children Forte Strawberry or Orange 200mg/5ml suspension, the patient is recommended to go to a doctor without delay. It is to be investigated whether there is an indication for an antimicrobial/antibiotic therapy.

The blood count should be checked regularly in long-term therapy.

The patient is to be instructed to inform a doctor at once and no longer to take Nurofen for Children Forte Strawberry or Orange 200mg/5ml suspension if one of the symptoms of hypersensitivity reactions occurs, which can happen even on first use, the immediate assistance of a doctor is required.

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.

| **System organ class** | **Frequency** | **Adverse Event** |
|---|---|---|
| Infections and infestations | Very rare | Exacerbation of infections related inflammation (e.g development of necrotizing fasciitis), in exceptional cases, severe skin infections and soft-tissue complications may occur during a varicella infection |
| 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 and bruising. In such cases, the patient should be advised to discontinue this medicinal product, to avoid any self-medication with analgesics or antipyretics and to consult a physician. |
| Immune System Disorders | Uncommon | Hypersensitivity reactions consisting of [1]:<br>Urticaria and pruritus |
| | Very rare | Severe hypersensitivity reactions. Symptoms could be: facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension (anaphylaxis, angioedema or severe shock). Exacerbation of asthma. |
| | Not known | Respiratory tract reactivity comprising asthma, bronchospasm or dyspnoea. |
| Psychiatric disorders | Very rare | Psychotic reactions, depression |
| | Uncommon | |

| | | |
|---|---|---|
| Nervous System Disorders | | Central nervous disturbances such as headache, dizziness, sleeplessness, agitation, irritability or tiredness |
| | Very Rare | Aseptic meningitis[2] |
| Eye disorders | Uncommoon | Visual disturbances |
| Ear and labyrinth disorders | Rare | Tinnitus |
| Cardiac Disorders | Very Rare | Cardiac failure, palpitations and oedema, myocardical infarction |
| Vascular Disorders | Very Rare | Hypertension, vasculitis |
| Gastrointestinal Disorders | Common | Gastrointestinal complaints such as abdominal pain, nausea and dyspepsia, diarrhoea, flatulence, constipation, heartburn, vomiting and slight gastro-intestinal blood losses that may cause anaemia in exceptional cases. |
| | Uncommon | Gastrointestinal ulcers, perforation or GI bleeding, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4), gastritis. |
| | Very Rare | Oesophagitis and formation of intestinal diaphragm-like strictures, pancreatitis. |
| Hepatobiliary Disorders | Very Rare | Hepatic dysfunction, hepatic damage, particularly in long-term theapy, hepatic failure, acute hepatitis. |
| Skin and Subcutaneous Tissue Disorders | Uncommon | Various skin rashes |
| | Very Rare | Severe forms of skin reactions such as bullous reactions including Stevens-johnson syndrome, erythema multiforme and toxic epidermal necrolysis, alopecia |

| | | |
|---|---|---|
| | Not known | Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)<br>Acute generalised exanthematous pustulosis (AGEP)<br><br>Photosensitivity reactions |
| Renal and Urinary Disorders | Rare | Kidney-tissue damage (papillary necrosis) and elevated urea concentration in the blood may also occur rarely; elevated uric acid concentrations in the blood. |
| | Very rare | Formation of oedemas, particularly in patients with arterial hypertension or renal insufficiency, nephrotic syndrome, interstitial nerphritis that may be accompanied by acute renal insufficiency. |
| Investigations | Rare | Decreased haemoglobin levels |

**Description of Selected Adverse Reactions**

[1]Hypersensitivity reactions have been reported following treatment with Ibuprofen. These may consist of (a) non-specific allergic reaction and anaphlaxis, (b) respiratory tract activity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and, more rarely, exfoliative and bullous dermatoses (including toxic epidermal necrolysis, Stevens Johnson Syndrome and erythema multiforme).

[2]The pathogenic mechanism of drug-induced aseptic meningitis is not fully understood. However, the available data on NSAID-related aseptic meningitis points to an immune reaction (due to a temporal relationship with drug intake, and disappearance of symptoms after drug discontinuation). Single cases of symptoms of aseptic meningitis (such as stiff neck, headache, nausea, vomiting, fever or clouding of consciousness) have been observed during treatment with Ibuprofen in patients with existing autoimmune disorders (such as systemic lupus erythematosus, mixed connective tissue disease).

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

**4.9 Overdose**

Ibuprofen doses in excess of 400mg/kg may cause symptoms of toxicity whilst a risk of toxic effects should not be excluded with a dose above 100 mg/kg.

Symptoms of overdosing

The symptoms of overdose can include nausea, vomiting, abdominal pain or more rarely diarrhoea. Nystagmus, blurred vision, tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning toxicity is seen in the central nervous system, manifesting as vertigo, dizziness, drowsiness, occasionally excitation and disorientation, loss of consciousness or coma. Occasionally patients develop convulsions. In serious poisoning metabolic acidosis may occur, hypothermia and hyperkalaemia may also occur and the prothombin time/INR may be prolonged, probably due to the interference with the actions of circulating clotting factors. Acute renal failure, liver damage, hypotension, respiratory depression and cyanosis may occur. Exacerbation of asthma is possible in asthmatics.

Management
No special antidote is available.

Management should be symptomatic and supportive and include the management of a clear airway and monitoring of cardiac and vital signs until stable. Oral administration of activated charcoal or gastric emptying should be considered if the patient presents within one hour of ingestion of a potentially toxic amount. If ibuprofen has already been absorbed, alkaline substances may be administered to promote the excretion of acid Ibuprofen in the urine. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. For asthma bronchodilators should be given. The local poisons centre should be contacted for medical advice.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-inflammatory and antirheumatic products, non steroids; propionic acid derivatives.
ATC code: M01AE01

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 symptomatic treatment of mild to moderate pain such as pain through toothache, headache, and in the 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 200 mg/5 ml Orange  contains Ibuprofen which showed in an open-label study an onset of antipyretic action after 15 minutes and decreases fever in children for up to 8 hours.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400 mg were taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-

dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 4.5).

**5.2 Pharmacokinetic properties**

No special studies on pharmacokinetics have been carried out in children. Literature data confirm that the absorption, metabolism and elimination of ibuprofen in children proceeds 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 active substance. 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 4.3)

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 4.3)

**5.3 Preclinical safety data**
The subchronic and chronic toxicity of ibuprofen in animal experiments showed up mainly in form of lesions and ulcerations in the gastro-intestinal tract. In vitro and in vivo studies gave no clinically relevant evidence of a mutagenic potential of ibuprofen. In studies in rats and mice no evidence of carcinogenic effects of ibuprofen was found.
Ibuprofen inhibited ovulation in rabbits and led to implantation disorders in various animal species (rabbit, rat, mouse). Experimental studies in rat and rabbit have shown that ibuprofen crosses the placenta. Following administration of maternotoxic doses, an increased incidence of malformations (ventricular septal defects) occurred in the progeny of rats.

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

| Nurofen for Children Forte Orange 200mg/5ml suspension | Nurofen for Children Forte Strawberry 200mg/5ml suspension |
|---|---|
| Maltitol Liquid | Maltitol Liquid |

| | |
|---|---|
| Glycerol | Glycerol |
| Xanthan gum | Xanthan gum |
| Sodium citrate | Sodium citrate |
| Citric acid monohydrate | Citric acid monohydrate |
| Orange Flavour 2M16014 | Strawberry Flavour 500244E |
| Sodium saccharin | Sodium saccharin |
| Sodium chloride | Sodium chloride |
| Polysorbate 80 | Polysorbate 80 |
| Domiphen Bromide | Domiphen Bromide |
| Purified water | Purified water |

**6.2 Incompatibilities**
Not applicable

**6.3 Shelf life**

The expiry date of the product is indicated on the packaging materials**.**
Shelf-life after first opening: 6 months

**6.4 Special precautions for storage**

Store below 25°C.

**6.5 Nature and contents of container**

Amber pigmented polyethylene terephthalate (PET) bottle with a child-resistant (CR) and tamper evident (TE) closure.

The pack contains a 5ml oral syringe with an orange polyethylene piston & a clear polypropylene barrel.

The bottle contains 30, 50, or 100 ml of oral suspension.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**
No special requirements.

**7. MANUFACTURER**
Reckitt Benckiser Healthcare (UK) Ltd
Dansom Lane
Hull
HU8 7DS
United Kingdom

**8. REGISTRATION HOLDER**
Reckit Benckister (Near east) LTD
Hanagar 6, Hod Hasharon

**9. REGISTRATION NUMBERS**
Nurofen for Children Forte Orange 200mg/5ml suspension: 165-23-35418
Nurofen for Children Forte Strawberry 200mg/5ml suspension: 165-24-35419

Revised on August 2021