PROFESSIONAL INFORMATION FOR NUROFEN FOR

CHILDREN 200 mg/ 5 mL SUSPENSION

SCHEDULING STATUS

S2

1. NAME OF MEDICINE

NUROFEN FOR CHILDREN STRAWBERRY 4 % *m/v*

NUROFEN FOR CHILDREN ORANGE 4 % *m/v*

Ibuprofen 200 mg per 5 ml oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of oral suspension contains ibuprofen 200 mg.

Contains sweeteners:

- Sodium saccharin: 11 mg per 5 ml
- Maltitol liquid: 2226 mg per 5 ml

Contains sodium: 9,35 per 5 ml

Contains preservative:

- Domiphen bromide 0,5 mg per 5 ml

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Oral suspension.

Off-white viscous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Children aged 7 to 12 years:

- Rheumatic or muscular pain, headache, dental pain, feverishness, symptoms of cold and influenza.

4.1 Posology and method of administration

For oral administration and short-term use only.

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see **section 4.4**).

For children weighing more than 20 kg, the daily dosage is 20 mg/kg bodyweight in divided doses. Using the dosing device provided this can be achieved as follows:

Child's age	**Single dose**	**Frequency of dosing in 24 hours**
7 to 9 years	200 mg (5 ml) (using the 5 ml end of the measuring spoon)	3 times
10 to 12 years	300 mg (7,5 ml) (using the measuring spoon twice (5 ml end and 2,5 ml end)	3 times

If the child's symptoms persist for more than three days, consult a doctor. **NUROFEN FOR CHILDREN 4 %** should only be given to children between 7-12 years of age and weighing more than 20 kg.

Leave at least four hours between doses and do not give more than the recommended amount in any 24 hours period.

For patients with sensitive stomachs it is recommended that **NUROFEN FOR CHILDREN 4 %** is taken during a meal.

If in children aged 7 to 12 years this **NUROFEN FOR CHILDREN 4 %** is required for more than three days, or if symptoms worsen, a doctor should be consulted. **NUROFEN FOR CHILDREN 4 %** should only be given to children who weigh more than 20 kg.

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 use.

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 medicines.
- History of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including **NUROFEN FOR CHILDREN 4 %**.

- In patients with active, or a history of recurrent ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)/perforations.
- In patients with cerebrovascular or other active bleeding.
- In patients with severe hepatic failure.
- In patients with renal failure, severe acute or chronic kidney disease.
- 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)
- 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 **NUROFEN FOR CHILDREN 4 %**.
- Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with **NUROFEN FOR CHILDREN 4 %** therapy. In view of the **NUROFEN FOR CHILDREN 4 %**'s inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS):

Drug Reaction with Eosinophillia and Systemic Symptoms has been reported in patients taking NSAIDs such **NUROFEN FOR CHILDREN 4 %**. Some of these events have been fatal or life threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophillia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue **NUROFEN FOR CHILDREN 4 %** and evaluate the patient immediately.

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.

Skin reactions:

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolyis have been reported. **NUROFEN FOR CHILDREN 4 %** should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Risk in pregnancy:

Regular use of NSAIDs such as **NUROFEN FOR CHILDREN 4 %** during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus in utero, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed and its duration increased.

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 medicines (eg misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose acetylsalicylic acid, or other medicines likely to increase gastrointestinal risk (see below and **section 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 medicines which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet medicines 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**).

Dermatological effects:

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis and acute generalised exanthematous pustulosis (AGEP), 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. **NUROFEN FOR CHILDREN 4 %** 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.

Masking of symptoms of underlying infections

NUROFEN FOR CHILDREN 4 % 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 4 %** is administered for pain or fever in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

Cardiovascular and cerebrosvascular effects:

Cases of Kounis syndrome have been reported. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction.
Clinical studies suggest that use of ibuprofen, particularly at a high dose (2 400 mg/day) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤ 1 200 mg/day) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension (systolic blood pressure greater than or equal to 140 mmHg and diastolic blood pressure greater than or equal to 90 mmHg), 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 (2 400 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 (2 400 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 4 %** 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 4 %**, regular checking of liver function, the kidney function, as well as full 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 medicines.

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.

NSAIDs may mask symptoms of infection and fever.

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 and adolescents.

Renal tubular acidosis and hypokalaemia:

Severe hypokalaemia and renal tubular acidosis have been reported due to prolonged use of ibuprofen at higher than recommended doses. Presenting signs and symptoms included reduced level of consciousness and generalised weakness. Ibuprofen induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis.

Excipient warnings:

NUROFEN FOR CHILDREN 4 % contains maltitol liquid.

Patients with rare hereditary problems of fructose intolerance should not take **NUROFEN FOR CHILDREN 4 %**.

NUROFEN FOR CHILDREN 4 % contains 1,87 mg sodium per 1 ml suspension. To be taken into consideration by patients on a controlled sodium diet.

Wheat starch in **NUROFEN FOR CHILDREN 4 %** 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 **NUROFEN FOR CHILDREN 4 %**.

4.5 Interaction with other medicines and other forms of interaction

NUROFEN FOR CHILDREN 4 % should be avoided in combination with:

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**).

Aspirin (acetylsalicylic acid):

Concomitant administration of **NUROFEN FOR CHILDREN 4 %** and aspirin 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 aspirin 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 aspirin cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use (see **section 5.1**).

NUROFEN FOR CHILDREN 4 % 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 medicines. 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, beta-receptor blocking medicine or angiotesin-II antagonists and medicines 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 perforation, 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 medicines 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.

Mifepristone:

NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Probenecid and sulfinpyrazone:

Medicines 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 %). These medicines should be administered with a few hours' interval.

4.6 Fertility, pregnancy and lactation

Pregnancy:

First trimester:

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

From the 20th week of pregnancy onward, **NUROFEN FOR CHILDREN 4 %** use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, **NUROFEN FOR CHILDREN 4 %** should not be given unless clearly necessary. If **NUROFEN FOR CHILDREN 4 %** 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. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to **NUROFEN FOR**

CHILDREN 4 % for several days from gestational week 20 onward. **NUROFEN FOR CHILDREN 4 %** should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

Second and third trimester:

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

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

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, **NUROFEN FOR CHILDREN 4 %** is contraindicated during the third trimester of pregnancy.

Breastfeeding:

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

Visual disturbances and dizziness have been reported. If affected, patients should not drive vehicles or operate machines.

4.8 Undesirable effects

The list of the following undesirable effects comprises all undesirable effects that have become known under treatment with **NUROFEN FOR CHILDREN 4 %**, 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 1 200 mg ibuprofen for oral dosage forms and a maximum of 1 800 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 **NUROFEN FOR CHILDREN 4 %** 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 (2 400 mg daily), may be associated with an 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 4 %**, 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 4 %** if one of the symptoms of hypersensitivity reactions occurs, which can happen even on first use, the immediate assistance of a medical practitioner is required.

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

System organ class	**Frequency**	**Adverse**
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 medical practitioner.
Immune system disorders	Uncommon	Hypersensitivity reactions consisting of 1. 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
Nervous system disorders	Uncommon	Central nervous disturbances such as headache, dizziness, sleeplessness, agitation, irritability or tiredness
	Very rare	Aseptic meningitis[2]
Eye disorders	Uncommon	Visual disturbances
Ear and labyrinth disorders	Rare	Tinnitus
Cardiac disorders	Very rare	Cardiac failure, palpitations and oedema, myocardial infarction, Kounis syndrome
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 therapy, 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), acute generalised exanthematous pustulosis (AGEP), 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 nephritis that may be accompanied by acute renal insufficiency.
	Not known	Ureteric colic, dysuria, acute renal failure, renal tubular acidosis[3]
Metabolism and nutrition disorders	Not known	Decreased appetite Hypokalaemia[3]
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 anaphylaxis, (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).
[3]Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of the ibuprofen component at higher than recommended doses.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Ibuprofen doses in excess of 400 mg/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 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 prothrombin 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.

Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see **sections 4.4** and **section 4.8**).

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

A 2.7 Antipyretic or antipyretic and anti-inflammatory analgesics.

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 4 %** 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 Pre-clinical 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

Polysorbate 80

Glycerol

Maltitol liquid

Saccharin sodium

Citric acid monohydrate

Sodium citrate

Xanthan gum

Sodium chloride

Domiphen Bromide

Purified water

NUROFEN FOR CHILDREN STRAWBERRY 4% *m/v:*

- Strawberry flavour 500244E contains natural & artificial flavourings, maltodextrin (wheat), modified starch E1450 (maize), Arabic gum E414.

NUROFEN FOR CHILDREN ORANGE 4% *m/v:*

Orange flavour 500244E (contains natural & artificial flavourings, maltodextrin (wheat), modified starch E1450 (maize), Arabic gum E414).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

100 ml and 150 ml bottles: 2 years

30 ml and 50 bottles: 18 months

Shelf-life after first opening: 6 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep well closed and protected from light

6.5 Nature and contents of container

Amber-coloured polyethyleneterephthalate (PET) bottle with a white high density polyethylene (HDPE) child-resistant closure.

The pack contains a polypropylene (PP) double-ended measuring spoon with a 2,5 ml bowl with 1,25 ml inner mark at one end and a 5 ml bowl at the other end.

The bottle contains 30, 50, 100 or 150 ml of oral suspension.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Reckitt Benckiser Pharmaceutical (Pty) Ltd

8 Jet Park Road

Elandsfontein

1601

8 REGISTRATION NUMBER(S)

NUROFEN FOR CHILDREN STRAWBERRY 4% *m/v:* *49/2.7/0178*

NUROFEN FOR CHILDREN ORANGE 4 % *m/v:* *49/2.7/0179*

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