Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nurofen for Children Six Plus Orange 200 mg/5 ml oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of oral suspension contains 40mg ibuprofen

Excipients with known effects:
Maltitol liquid 2226 mg per 5 ml
Sodium 9.18 mg (0.40 mmol) per 5 ml
Wheat starch 15.4 mg, containing no more than 0.315 µg gluten per 5 ml
For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Oral suspension.

An off-white, viscous suspension with an orange flavour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology:
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 weight (age)	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 and 2.5ml)	3 times

Doses should be given approximately every 6 to 8 hours.
Not intended for children under 6 years of age or under 20kg.

For short-term use only.
If symptoms worsen medical advice should be sought.

If this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted.

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

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.

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

4.3 Contraindications

Nurofen for Children is contraindicated

- 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 (e.g. bronchospasm, asthma, rhinitis, angioedem 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 minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see GI and cardiovascular risks below).

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

- Hayfever, 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.

Masking of symptoms of underlying infections
Nurofen for Children 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 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.

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 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 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 medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents 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 cutaneous skin reactions (SCARs)
Severe cutaneous adverse reactions (SCARs) including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with the use of ibuprofen (see Section 4.8). Most of these reactions occurred within the first month. If signs and symptoms suggestive of these reactions appear, ibuprofen should be withdrawn immediately and an alternative treatment considered (as appropriate).
Exceptionally, varicella can be at the origin of serious cutaneous and soft tissues infectious complications. 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.
Cases of Kounis syndrome have been reported in patients with Nurofen for Children. 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.

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.

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.

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 analgesic drug substances, can lead to lasting renal lesions with the risk of renal failure (analgesic nephropathy).
There is a risk of renal impairment in dehydrated children.

Product Specific warnings:
This product contains maltitol liquid.
Patients with rare hereditary problems of fructose intolerance should not take this medicine.
Due to the maltitol liquid content this medicine may have a mild laxative effect.

The calorific value is 2.3 kcal/g maltitol

This medicinal product contains 27.54 mg sodium per 15 ml suspension (= 1.836 mg sodium per 1 ml suspension). To be taken into consideration by patients on a controlled sodium diet.

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).

4.5 Interaction with other medicinal products and other forms of interaction

Ibuprofen should be avoided in combination with:

Other NSAIDs including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs 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 (like other NSAIDs) should be used with caution in combination with:
Antihypertensives, (ACE inhibitors, betareceptor blocking medicines 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 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. 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 Nurofen for Children with digoxin preparations may increase serum levels 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 Nurofen for Children and potassium-sparing diuretics may lead to hyperkalaemia (check of serum potassium is recommended)
Phenytoin:
The concomitant use of Nurofen for Children with phenytoin preparations may increase serum levels 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 Nurofen for Children 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 agents 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:

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.
From the 20th week of pregnancy onward, ibuprofen 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 construction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, 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. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to ibuprofen for several days from gestational week 20 onward. Treatment should be discontinued if oligohydramnios or ductus arteriosus constriction are found.
During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension)
- renal dysfunction (see above)

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 dosage 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, 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 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]
		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
	Not known	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 cutaneous adverse reactions (SCARs) (including erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome 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 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 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 a immune reaction (due to a temporal relationship with drug intake, and disappearance of symptoms after drug discontinuation). Of note, 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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

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

(A) 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. Prolonged use at higher than recommended doses or overdose may result in renal tubular acidosis and hypokalaemia. In serious poisoning hyperkalaemia and metabolic acidosis, may 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. Exacerbation of asthma is possible in asthmatics.

(B) 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. Consider oral administration of activated charcoal or gastric emptying 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. Give bronchodilators for asthma. 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 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 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 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

Citric acid monohydrate
Sodium citrate
Sodium chloride
Saccharin sodium
Polysorbate 80
Domiphen Bromide
Maltitol Liquid
Glycerol
Xanthan gum
Orange Flavour (containing wheat starch)
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

50ml, 100ml, 150ml and 200ml bottle: 2 years
30ml bottle: 1 year
Shelf-life after first opening the bottle: 6 months

6.4 Special precautions for storage

Do not store above 25°C.

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 measuring device

polypropylene (PP) double-ended measuring spoon with a 2.5ml bowl with 1.25ml inner mark at one end and a 5ml bowl at the other end.
The bottle contains 30, 50, 100, 150ml or 200ml of oral suspension.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Reckitt Benckiser Ireland Ltd
7 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0979/056/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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