PHYSICIAN'S PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

Nurofen for Children Suppositories 60 mg
Nurofen for Children Suppositories 125 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Nurofen for Children Suppository 60 mg contains 60 mg ibuprofen.
Each Nurofen for Children Suppository 125 mg contains 125 mg ibuprofen.

For the full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Suppositories
Nurofen for Children Suppositories 60 mg- Torpedo Shaped, unbroken, almost white to white smooth suppository
Nurofen for Children Suppositories 125 mg- Torpedo Shaped, unbroken, white to yellowish white smooth suppository

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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For the symptomatic treatment of mild to moderate pain, and for the symptomatic treatment of fever.

4.2 Posology and method of administration

Rectal use.
Use in children under 6 months of age requires prescription.

Posology

For short term use only.

Do not use this product in children under 3 months of age without medical advice.

Do not use this product in children weighing less than 6 Kg.

Nurofen for children suppositories 125 mg are not suitable for infants weighing less than 12.5 kg (approximately 2 years of age), as suppositories containing less active substance are needed (see also section 4.3).

The maximum total daily dose of the product is 20 - 30 mg per kg of body weight, divided into 3-4 single doses. This can be achieved as follows:

Age	Body weight (kg)	Recommended Dosage
Infants 3-9 months weighing more than 6 kg	6-8	60 mg up to 3 times in 24 hours, leaving 6-8 hours between doses
9 months-2 years	8-12.5	60 mg up to 4 times in 24 hours, leaving 6 hours between doses
Children 2-4 years	12.5-17	125 mg up to 3 times in 24 hours, leaving 6-8 hours between doses

Children 4-6 years	17-20.5	125 mg up to 4 times in 24 hours, leaving 6 hours between doses

For infants aged 3-5 months, medical advice should be sought if symptoms worsen or not later than 24 hours if symptoms persist. If in children aged from 6 months and in adolescents this medicinal product is required for more than 3 days, or if symptoms worsen, a doctor should be consulted.

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

Method of administration

For rectal use only.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients with severe hepatic failure, severe renal failure or severe heart failure (see section 4.4).

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active, or history of recurrent peptic ulcer/ haemorrhage (two or more distinct episodes of proven ulceration or bleeding or other gastrointestinal disorders).

Patients with a history of hypersensitivity reactions (e.g bronchospasm, asthma, rhinitis, angioedema or urticaria) associated with acetylsalicylic acid (aspirin) or other non-steroidal anti-inflammatory drugs (NSAIDs).

During the last trimester of pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Masking of symptoms of underlying infections :
Nurofen for Children Suppositories 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 Suppositories 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.

The use of Nurofen for Children Suppositories with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms (See section 4.2, and 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.

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

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, 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 (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs 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 stages 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 (aspirin) (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving Nurofen for Children Suppositories, 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 their conditions may be exacerbated (see section 4.8 – undesirable effects).

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

Cardiovascular and cerebrovascular effects

Clinical trial and epidemiological data suggest that use of ibuprofen, particularly at high doses (2400mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. < 1200mg daily) is associated with an increased risk of myocardial infarction.

Caution is required in patients with renal impairment (see section 4.3) since renal function may deteriorate. In patients with renal impairment, renal function should be monitored as it may deteriorate following the use of NSAIDs.

Caution is required in patients with hepatic impairment (see section 4.3 and 4.8).

Elderly patients are particularly susceptible to the adverse effects of NSAIDs. Prolonged use of NSAIDs in the elderly is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

As NSAIDs can interfere with platelet function, they should be used with caution in patients with idiopathic thrombocytopenic purpura (ITP), intracranial haemorrhage and bleeding diathesis.

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 generalized exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. Nurofen for Children Suppositories should be discontinued at the first appearance of signs and symptoms of severe skin reaction, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissue 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 Nurofen for Children Suppositories in case of varicella.

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

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

Caution is advised in patients with systemic lupus erythematosus as well as those with

connective tissue disease (see section 4.8).
Caution is also required in patients with disorders of the anus or rectum. There is a risk of renal impairment in dehydrated children.

4.5 Interaction with other medicinal products and other forms of interactions

Ibuprofen should be avoided in combination with:

Acetylsalicylic acid (Aspirin): unless low-dose Acetylsalicylic Acid (Aspirin), (not above 75 mg daily), has been advised by a doctor, as this may increase the risk of adverse reactions (see section 4.4). Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid (aspirin) on platelets aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding the extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

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

It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.

Care should be taken in patients treated with any of the following drugs as interactions have been reported:

Anti-hypertensives (ACE inhibitors and Angiotensin II Antagonists) and diuretics: NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor, 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. These interactions should be considered in patients taking ibuprofen concomitantly with ACE inhibitors or angiotensin II antagonists.
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.

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

Anti-coagulants: NSAIDs may enhance the effects of anticoagulants, 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).

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels.

Lithium: decreased elimination of lithium. **Methotrexate:**

decreased elimination of methotrexate. **Cyclosporin:** Increased

risk of nephrotoxicity with NSAIDs.

Aminoglycosides: reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations.

Probenecid: reduction in metabolism and elimination of NSAID and metabolites.

Oral hypoglycemic agents: inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia.

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

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

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with Zidovudine. There is evidence of an increased risk of haema rthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is insufficient experience about the safety of use of ibuprofen in humans during pregnancy. As the influence of prostaglandin synthesis inhibition is unclear, it is recommended not to use ibuprofen during the first six months of pregnancy.

In the last trimester of pregnancy use of ibuprofen is contraindicated. Due to the mechanism of action, inhibition of uterine contractions, premature closure of ductus arteriosus and pulmonary hypertension of the neonate, an increased bleeding tendency in mother and child and increased formation of oedema in the mother could occur.

Breast-feeding

Ibuprofen and its metabolites can pass in very small concentrations (0.0008% of the maternal dose) into the breast milk. No harmful effects to infants are known, so it is not necessary to interrupt breast-feeding for short-term treatment with the recommended dose for mild to moderate pain and fever.

Fertility

See section 4.4 on Special Warnings and Precautions for use regarding female fertility

4.7 Effects on ability to drive and use machines

Nurofen for Children Suppositories has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The list of the following adverse effects relates to those experienced with ibuprofen at OTC doses (maximum 1200mg ibuprofen per day), for short-term use. In the treatment of chronic conditions, under long-term treatment, additional adverse effects may occur.

Adverse events which have been associated with ibuprofen are given below, tabulated by system organ class and frequency.

The frequencies are defined as follows:

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1000 to <1/100)

Rare (≥1/10000 to <1/1000) Very

Rare (<1/10000)

Not known (cannot be estimated from the available data)

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

System Organ Class	Frequency	Adverse Event
Blood and Lymphatic System Disorders	Very rare	Haematopoietic disorders[1]
Immune System Disorders	Uncommon	Hypersensitivity reactions with Urticaria and pruritus[2]
	Very rare	Severe hypersensitivity reactions, including facial, tongue and throat swelling, dyspnoea, tachycardia and hypotension (anaphylaxis, angioedema or severe shock)[2]
Nervous System Disorders	Uncommon	Headache
	Very rare	Aseptic meningitis[3]
Cardiac Disorders	Very rare	Cardiac failure and oedema[4]
Vascular Disorders	Very rare	Hypertension[4]
Respiratory, Thoracic and Mediastinal Disorders	Very rare	Respiratory and tract reactivity compromising asthma, aggravated asthma, bronchospasm or dyspnoea[2]
Gastrointestinal Disorders	Uncommon	Abdominal pain, nausea and dyspepsia[5]
	Rare	Diarrhoea, flatulence, constipation and vomiting
	Very rare	Peptic ulcer, gastrointestinal perforation or gastrointestinal haemorrhage, melaena and haematemesis[6]. Exacerbation of colitis and Crohn's disease[7]. Mouth ulceration and gastritis
Hepatobiliary Disorders	Very rare	Liver disorder[8] Cholestatic jaundice, hepatitis, elevation of serum enzymes
Skin and Subcutaneous Tissue Disorders	Uncommon	Skin rash[2]
	Very rare	Severe forms of skin reactions such as erythema multiforme, epidermal necrolysis and Stevens-Johnson syndrome[2]
	Not known	DRESS syndrome: Drug reaction with eosinophilia and systemic symptoms Acute generalised exanthematous pustulosis (AGEP)
Renal and Urinary Disorders	Very rare	Acute renal failure[9]

Investigations	Very rare	Haemoglobin decreased, urea renal clearance decreased
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

Description of Selected Adverse Reactions

[1]Examples include anaemia, leucopenia, thrombocytopenia, pancytopenia and agranulocytosis. First signs are fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.

[2]Hypersensitivity reactions: These may consist of (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract reactivity, including asthma, aggravated asthma, bronchospasm, and dyspnoea, or (c) various skin reactions, including pruritus, urticaria, purpura, angioedema and, more rarely, exfoliative and bullous dermatoses, including toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme.

[3]The pathogenic mechanism of drug-Induced aseptic meningitis is not fully understood. However, the available data on NSAID-related aseptic meningitis points to a hypersensitivity reaction (due to a temporal relationship with drug intake, and disappearance of symptoms after drug discontinuation). Of note, in patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic meningitis such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed.

[4]Clinical trial and epidemiological data suggest that use of ibuprofen (particularly at high doses 2400mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke), (see section 4.4).

[5]The adverse events observed most often are gastrointestinal in nature.

[6]Sometimes fatal, particularly in the elderly (see section 4.4).

[7]See section 4.4.

[8]Especially in long-term treatment.

[9]Decrease of urea excretion and oedema can occur. Papillary necrosis, especially in long-term use, and increased serum urea concentrations have been reported.

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

A dose in excess of 200 mg/kg carries a risk of causing toxicity.

Symptoms of Overdosing

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, abdominal pain, or more rarely diarrhoea. Tinnitus, headache, nystagmus, blurred vision, hypotension and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as dizziness, drowsiness, loss of consciousness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning metabolic acidosis may occur and the prothrombin time/INR may be prolonged, probably due to interference with

the actions of circulating clotting factors. Acute renal failure and liver damage may occur. Exacerbation of asthma is possible in asthmatics.

Therapeutic Measure in Overdosing

Patients should be treated symptomatically as required. Use supportive care where appropriate. Management should include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma. No specific antidote is available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-inflammatory and anti-rheumatic products, non-steroids, propionic acid derivative; **ATC code:** M01AE01

Ibuprofen is a 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 efficacy of ibuprofen has been demonstrated in fever and in pain associated with headache, toothache and dysmenorrhoea. Furthermore it has been demonstrated in patients with pain and fever associated with cold and flu and in pain models such as sore throat, muscular pain, soft tissue injury, backache.

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

5.2 Pharmacokinetic properties

After rectal administration, ibuprofen is absorbed quickly and almost completely, and is rapidly distributed throughout the whole body. Median peak plasma concentrations are seen 0.75 hours after use Nurofen for children suppository.

Ibuprofen is extensively bound to plasma proteins.

Ibuprofen is metabolised in the liver to two major inactive metabolites and these, together with unchanged ibuprofen, are excreted by the kidney either as such or as conjugates. Excretion by the kidney is both rapid and complete. The elimination half life is approximately 2 hours.

No special pharmacokinetic studies have been carried out in children. However, pharmacokinetic parameters of ibuprofen in children are comparable with those in adults.

5.3 Preclinical safety data

The toxicity of ibuprofen in animal experiments was observed as lesions and ulcerations in the gastrointestinal tract. Ibuprofen did not show a mutagenic potential in vitro and was not carcinogenic in rats and mice. Experimental studies have demonstrated that ibuprofen crosses the placenta, but there is no evidence of any teratogenic action.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Nurofen for Children Suppositories 60 mg: Hard fat 1 (Witespol H15), Hard Fat 2 (Witespol H 45).
Nurofen for Children Suppositories 125 mg: Hard Fat

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of the container

Aluminum/Polyethylene blisters containing 10, suppositories.

6.6 Special precaution for disposal and other handling

None.

7. MANUFACTURER

Reckitt Benckiser Healthcare Int. Ltd., Danson Lane, Hull, East Yorkshire, UK.

8. REGISTRATION HOLDER

Reckitt Benckiser (Near East) Ltd., HaNagar 6, Hod HaSharon 45420.

9. REGISTRATION NUMBER

Nurofen for Children Suppositories 60 mg: 142-88-31900-00
Nurofen for Children Suppositories 125 mg: 142-89-32016-01

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