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| **Submissions to the Medicines Classification Committee for the Reclassification of** **LIQUID IBUPROFEN****100mg/5ml****100 ml BOTTLES** |
| **Present Classification:** Pharmacy-Only Medicine**Sought Classification:** General Sale Medicine |

**Date prepared:** 22 July 2013

**Sponsor:** New Zealand Retailers Association (on behalf of Grocery Retailers)

**Applicant:** Pharmaceutical Solutions Ltd

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| Executive Summary |

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAIDs) commonly used to relieve fever and pain. The scenario around Ibuprofen is also similar to paracetamol in which certain packs of Ibuprofen are readily available for adults in the grocery channel; however there is no liquid Ibuprofen available for children 3 months and over.

Liquid ibuprofen has been registered in New Zealand since 9 Jun 19951.

The purpose of this application is to seek reclassification of liquid ibuprofen with recommended daily dose of not more than 1.2 grams in the manufacturer’s original pack containing not more than 4 grams of ibuprofen and not more than 100 ml of product from ‘Pharmacy Only’ medicine to ‘General Sale’ medicine.

The current classification for a liquid ibuprofen, with a recommended daily dose of not more than 1.2 grams for the relief of pain and reduction of fever or inflammation when sold in the manufacturer’s original pack containing not more than 8 grams is a ‘Pharmacy Only’ medicine.

Ibuprofen in divided solid dosage forms are currently classified as ‘General Sale’ medicine when containing 200 milligrams or less per dose form with a recommended daily dose of not more than 1.2 grams and when sold in the manufacturer's original pack containing not more than 25 dose units per pack. The difference in legal status is therefore based on packaging format and dosage form.

The product is intended for short-term oral administration in children from 3 months to 12 years, for the reduction of fever, including post-immunisation pyrexia and temporary relief of mild-to-moderate pain associated with teething, toothache, earache, sore throats, headache, minor aches, sprains and strains and cold and flu. It is also an option for parents/caregivers who have pre-teen children who have difficulty swallowing capsules or tablets.

This reclassification application proposes that the 100 ml bottle of liquid ibuprofen for children is reclassified from ‘Pharmacy Only’ medicine to ‘General Sale’ in line with the legal classification for the solid dose forms currently classified as ‘General Sale’ medicine.

Liquid Ibuprofen is available as ‘General Sale’ in UK, Canada and USA; and as ‘Pharmacy Only’ in Australia.

The intention of this reclassification is to provide the consumer (parents/caregivers) with the convenience and choice of purchasing ibuprofen in liquid form for their child/children for the short term treatment to relieve pain, inflammation and fever in an accessible environment which is not limited in hours of availability and/or location as it is at Pharmacy level.

Supermarkets generally open much longer hours than pharmacies18. Aside from those in malls, few pharmacies open on Sundays. Grocery stores are more prevalent in rural areas where there may be no other options for quick access to these medicines. The latest information sourced by the NZ Retailers Association still confirms that supermarkets opening hours are two times longer on average compared to pharmacies.

This reclassification application chose Nurofen for Children as the reference product as it is the ‘Over the Counter’ (OTC) market leader in children’s analgesia for ibuprofen suspension. The proposed reclassification will incorporate indications and warnings consistent with the current Nurofen for Children in the market for ‘Pharmacy Only’ medicine.

Ibuprofen is one of the most frequently used OTC analgesics/antipyretics. Its safety and efficacy in children have been reviewed extensively and the safety profile of ibuprofen is well established. Side effects are also generally well tolerated. The proposed classification for liquid ibuprofen is not expected to increase the potential risk of adverse events nor the potential for abuse or misuse.

All liquid ibuprofen products currently listed on the Medsafe website (June 2013)1;

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| **Trade Name** | **Sponsor** | **Registration situation** |
| Advil Childrens Pain & Fever Relief Oral suspension, 100mg/5ml (Pharmacy only) | Pfizer New Zealand Limited | Consent givenApproval date: 14/10/2010 |
| Advil Infant's Pain & Fever Relief Oral suspension, 200mg/5ml (Pharmacy only) | Pfizer New Zealand Limited | Consent givenApproval date: 28/7/2011 |
| Fenpaed Oral suspension, 100mg/5ml, Pharmacy-only (Pharmacy only) | AFT Pharmaceuticals Ltd | Consent givenApproval date: 8/7/2004 |
| Ibuprofen Oral suspension, 100mg/5ml, Ethics (Pharmacy only) | Multichem NZ Limited | Consent givenApproval date: 25/11/2010 |
| Ibuprofen for Children Oral suspension, 100mg/5ml, Arrowcare (Pharmacy only) | Arrow Pharmaceuticals (NZ) Limited | Consent givenApproval date: 14/3/2013 |
| Nurofen for Children Oral suspension, 20mg/ml (Pharmacy only) | Reckitt Benckiser (New Zealand) Limited | Consent givenApproval date: 9/6/1995 |
| Nurofen for Children 5 - 12 years Oral suspension, 40mg/ml, (Concentrated Strawberry) (Pharmacy only) | Reckitt Benckiser (New Zealand) Limited | Consent givenApproval date: 20/7/2012 |
| Nurofen for Children 5-12 years Oral suspension, 40mg/ml, (Concentrated Orange) (Pharmacy only) | Reckitt Benckiser (New Zealand) Limited | Consent givenApproval date: 20/7/2012 |
| Nurofen for Children Baby 3+ months Oral suspension, 200mg/5ml, Concentrated, Orange (Pharmacy only) | Reckitt Benckiser (New Zealand) Limited | Consent givenApproval date: 23/12/2010 |
| Nurofen for Children Baby 3+ months Oral suspension, 200mg/5ml, Concentrated, Strawberry (Pharmacy only) | Reckitt Benckiser (New Zealand) Limited | Consent givenApproval date: 23/12/2010 |
| Nurofen for Children Infant Drops Oral suspension, 200mg/5ml (Pharmacy only) | Reckitt Benckiser (New Zealand) Limited | Consent givenApproval date: 23/12/2010 |
| Nurofen for Children Strawberry Flavour Oral suspension, 20mg/ml (Pharmacy only) | Reckitt Benckiser (New Zealand) Limited | Consent givenApproval date: 19/1/2006 |
| Your Pharmacy Ibuprofen Suspension Oral suspension, 20mg/ml (Pharmacy only) | Orion Laboratories (NZ) Ltd | Consent givenApproval date: 24/11/2011 |

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| Part A |

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| A.1. International Non-proprietary Name (or British Approved Name or US Adopted Name) of the medicine |

**Name:** Ibuprofen

**Chemical structure:**

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**Molecular Formula:** C13H18O2

**Molecular Weight:** 206.29 g/mol

**CAS number:** 15687-27-1

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| A.2. Proprietary name(s) |

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| Sponsor | Product1 |
| Reckitt Benckiser (New Zealand) Limited | Nurofen for Children Oral suspension 20mg/ml |
| Nurofen for Children (Strawberry Flavour) Oral suspension 20mg/ml |

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| A.3. Name of company/organisation/individual requesting reclassification |

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| A.4. Dose form(s) and strength(s) for which a change is sought |

Our proposal is to reclassify Ibuprofen supplied in undivided liquid form for oral use with a recommended maximum daily dose of not more than 1.2 grams for the relief of pain and reduction of fever or inflammation when sold in the manufacturer's original pack containing not more than 4 grams of ibuprofen and not more than 100 ml of product, from ‘Pharmacy Only’ medicine to ‘General Sale’ medicine.

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| A.5. Pack size and other qualifications |

This reclassification request is to permit 100 ml liquid ibuprofen (100mg/5ml) to become a ‘General Sale’ medicine, when labelled for use in children from 3 months.

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| A.6. Indications for which change is sought |

This proposal does not increase the range of indications or dosage recommendations for the use of ibuprofen beyond those for existing liquid Nurofen for Children.

No change is sought in relation to indications. The current approved indications for Nurofen for Children in New Zealand are:

* Temporary relief of pain and/or inflammation associated with teething, toothache, earache, sore throats, headache, minor aches, sprains and strains, cold and flu.
* Reduction in temperature for up to 8 hours including fever caused by immunization

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| A.7. Present classification of medicine |

Ibuprofen in liquid form is currently classified as a ‘Pharmacy Only’ medicine in New Zealand and the conditions are provided below:

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| Classification2 | Conditions (if any) |
| Pharmacy Only | **for oral use in liquid form with a recommended daily dose of not more than 1.2 grams for the relief of pain and reduction of fever or inflammation when sold in the manufacturer's original pack containing not more than 8 grams**; for oral use in solid dose form containing not more than 200 milligrams per dose form and with a recommended daily dose of not more than 1.2 grams when sold in the manufacturer's original pack containing not more than 100 dose units; except in divided solid dosage forms for oral use containing 200 milligrams or less per dose form with a recommended daily dose of not more than 1.2 grams and when sold in the manufacturer's original pack containing not more than 25 dose units |

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| A.8. Classification sought |

This application requests reclassification to ‘General Sale’ medicine status.

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| Classification | Conditions (if any) |
| General Sale | for external use; in divided solid dosage forms for oral use containing 200 milligrams or less per dose form with a recommended daily dose of not more than 1.2 grams and when sold in the manufacturer's original pack containing not more than 25 dose units per pack; **in undivided liquid form for oral use with a recommended maximum daily dose of not more than 1.2 g for the relief of pain and reduction of fever or inflammation when sold in the manufacturer's original pack containing not more than 4 grams and not more than 100 ml of product.** |

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| A.9. Classification status in other countries (especially Australia, UK, USA, Canada)  |

Liquid Ibuprofen is available as General Sale in UK, Canada and USA; and as Pharmacy-only in Australia. The conditions for General Sale in the UK and Canada are provided below.

| Country | Conditions (if any) |
| --- | --- |
| Australia3 | **Schedule 2 (**Pharmacy Medicine**)**IBUPROFEN in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen:1. **in liquid preparations when sold in the manufacturer‘s original pack containing 8 grams or less of ibuprofen**; or
2. in divided preparations, each containing 200 mg or less of ibuprofen, in packs of not more than 100 dosage units **except** when:
3. as the only therapeutically active constituent other than an effervescent agent;
4. packed in blister or strip packaging or in a container with a child-resistant closure;
5. in a primary pack containing not more than 25 dosage units;
6. not labelled for the treatment of children 6 years of age or less; and
7. compliant with the requirements of the *Required Advisory Statements for Medicine Labels*.
 |
| UK4 | Liquid**Max strength 2% (100mg in 5ml).** For the treatment of rheumatic or muscular pain, headache, dental pain, feverishness, or symptoms of colds and influenza. **For children under the age of 12 years****Max dose: 200mg. Max daily dose: 800mg.** Max pack: Individual unit doses of not more than 5ml each in a pack containing not more than 20 doses *OR* multidose containers containing not more than 100ml of product. |
| Canada5 | Ibuprofen and its salts, containing 400 mg or less per oral dosage unit (when sold in package sizes of up to 18,000 mg)  |
| USA7 | Ibuprofen in suspension formulation for children’s formulations have been marketed OTC since 1998. |

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| A.10. Extent of usage in New Zealand and elsewhere (e.g. sales volumes) and dates of original consent to distribute |

The Nurofen brand of ibuprofen in liquid form for children has been registered in New Zealand from as early as 1995.

There are currently two 20mg/ml liquid Nurofen products suitable for use in children ages 3 months to 12 years registered and marketed in NZ and are listed below:

|  |  |  |  |
| --- | --- | --- | --- |
| Sponsor | Product1 | Marketed pack sizes | Approval date |
| Reckitt Benckiser (New Zealand) Limited | Nurofen for Children Oral suspension 20mg/ml | 100ml, 200ml | 9/06/1995 |
| Nurofen for Children (Strawberry Flavour) Oral suspension 20mg/ml | 100ml, 200ml | 19/01/2006 |

Usage in New Zealand:

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| **National Pharmacy** |
| **MAT To 24/02/13** |
|   | Dollars | Volume (ml) | Units |
| Nurofen Children Orange 100ml | 31,626  | 191,800  | 1,918  |
| Nurofen Children Orange 200ml | 403,175  | 3,119,200  | 15,596  |
| Nurofen Children Strawberry 100ml | 481,392  | 2,743,500  | 27,435  |
| Nurofen Children Strawberry 200ml | 655,638  | 5,106,400  | 25,532  |
| **Total Nurofen For Children** | **1,571,832**  | **11,160,900**  | **70,481**  |
|  |  |  |  |
| **National Pharmacy** |
| **Year 2012** |
|   | Dollars | Volume | Units |
| Nurofen Children Orange 100ml | 53,885  | 321,386  | 3,214  |
| Nurofen Children Orange 200ml | 402,042  | 3,112,886  | 15,564  |
| Nurofen Children Strawberry 100ml | 468,820  | 2,679,957  | 26,800  |
| Nurofen Children Strawberry 200ml | 645,407  | 5,032,114  | 25,161  |
| **Total Nurofen For Children** | **1,570,154**  | **11,146,343**  | **70,739**  |
|  |  |  |  |
| **National Pharmacy** |
| **Year 2011** |
|   | Dollars | Volume | Units |
| Nurofen Children Orange 100ml | 213,854  | 1,244,743  | 12,447  |
| Nurofen Children Orange 200ml | 348,507  | 2,669,257  | 13,346  |
| Nurofen Children Strawberry 100ml | 394,798  | 2,290,000  | 22,900  |
| Nurofen Children Strawberry 200ml | 561,313  | 4,386,800  | 21,934  |
| **Total Nurofen For Children** | **1,518,472**  | **10,590,800**  | **70,627**  |

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| A.11. Labelling or draft labelling for the proposed new presentation(s) |

The proposed liquid products will be labelled with the same directions for use, indications and warning statements as the Nurofen for Children oral suspension currently marketed in New Zealand, only the ‘Pharmacy only medicine’ statement is to be removed.

There is no requirement for different dosing instructions or indications for General Sale. It is important to ensure consistency of information across the Nurofen for Children range so that parents accustomed to using the product are not confused with conflicting information on packs bought in differing outlets.

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| A.12. Proposed warning statements if applicable |

The proposed liquid product will be labelled with the same warning statement as the Nurofen for Children oral suspension currently marketed in New Zealand.

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| BEFORE USE:* Most asthmatics can take Nurofen for Children but if your child is sensitive to pain relievers, do not use this product. If you are unsure, check with your pharmacist or doctor.
* If your child is receiving any other regular treatment or medicines consult your doctor.
* In adults this product is not recommended for use by pregnant women except on a doctor’s advice. Do not use in the last three months of pregnancy.

DO NOT GIVE TO BABIES OR CHILDREN WHO:Have impaired kidney function, stomach disorders or stomach ulcers, are allergic to aspirin, ibuprofen or other anti-inflammatory medicines, or are suffering dehydration. |

The above label warnings meet the labelling requirements stated in the Medsafe label statement database for ibuprofen liquid.

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| A.13. Other products containing the same active ingredient(s) and which would be affected by the proposed change |

There are currently 11 other ‘Pharmacy Only’ liquid presentations with a recommended daily dose of 1200 mg or less of ibuprofen, in 100 ml bottle containing not more than 4 g of ibuprofen, suitable for use in children registered in NZ and are listed below:

|  |  |  |  |
| --- | --- | --- | --- |
| Sponsor | Product1 | Pack sizes | Approval date |
| Pfizer New Zealand Limited | Advil Childrens Pain & Fever Relief Oral suspension 100mg/5ml | 100ml, 200ml | 14/10/2010 |
| Advil Infant's Pain & Fever Relief Oral suspension, 200mg/5ml | 40ml | 28/7/2011 |
| AFT Pharmaceuticals Ltd | Fenpaed Oral suspension 100mg/5ml | 100ml, 150ml, 200ml | 8/07/2004 |
| Arrow Pharmaceuticals (NZ) Limited | Ibuprofen for Children Oral suspension, 100mg/5ml, Arrowcare (Pharmacy only) | 100ml, 200ml | 14/3/2013 |
| Reckitt Benckiser (New Zealand) Limited | Nurofen for Children 5 - 12 years (Concentrated Strawberry) Oral suspension 40mg/ml | 100ml | 20/07/2012 |
| Nurofen for Children 5-12 years (Concentrated Orange) Oral suspension 40mg/ml | 100ml | 20/07/2012 |
| Nurofen for Children Baby 3+ months Oral suspension, 200mg/5ml, Concentrated, Orange | 30ml, 50ml | 23/12/2010 |
| Nurofen for Children Baby 3+ months Oral suspension, 200mg/5ml, Concentrated, Strawberry | 30ml, 50ml | 23/12/2010 |
| Nurofen for Children Infant Drops Oral suspension, 200mg/5ml | 30ml, 50ml | 23/12/2010 |
| Nurofen for Children Oral suspension, 20mg/ml (reference product) | 100ml, 200ml | 9/6/1995 |
| Nurofen for Children Strawberry Flavour Oral suspension, 20mg/ml (reference product) | 100ml, 200ml | 19/1/2006 |

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| Part B |

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| B.1. A statement of the benefits to both the consumer and to the public expected from the proposed change |

Ibuprofen has been available internationally for more than 50 years, firstly as prescription medicine then as a non-prescription medicine. Currently liquid ibuprofen is available for self-selection by patients in a pharmacy. The Nurofen for Children product range has been available at this level of classification for several years and no significant safety concerns have arisen8.

Ibuprofen is a well-established non-steroidal anti-inflammatory drug (NSAIDs) used to relieve fever and pain and unlike paracetamol is a known anti-inflammatory. The scenario around Ibuprofen is similar to paracetamol in which certain packs of Ibuprofen are readily available for adults in the grocery channel; however there is no liquid Ibuprofen available for children.

Pharmacy operating hours are generally short compared to operating hours of supermarkets. This can limit the access of patients to required medication. The reclassification of liquid ibuprofen (100mg/5ml) bottle to a General Sale Medicine will allow patients easier and more convenient access to an effective and safe short term therapy. A study in New Zealand by the NZ Retailers Association concluded that supermarkets were open for 101.5 hours per week on average and pharmacies were open 55.1 hours per week on average in the same areas examined 18. The latest information sourced by the NZ Retailers Association still confirms that supermarkets opening hours are two times longer on average compared to pharmacies. This reclassification enables access to parents with after hour emergencies. The dosing chart on the pack includes both age and weight guidelines to provide specific instruction for parents to follow.

Contact details for consumers available on the pack to seek medical advice. There are sufficient warnings to alert parents and caregivers when not to use ibuprofen for their children and also when to seek medical attention - before use, if the child has certain medical conditions or is allergic to ibuprofen or other pain relievers; and after use, to seek medical attention if symptoms still persists.

This change also means that consumers in New Zealand will have the same access to liquid ibuprofen as consumers in the United States, the United Kingdom and Canada.

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| B.2. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated |

The indication for use and dose form proposed in this reclassification application for Nurofen for Children oral suspension are essentially identical to those for Nurofen for Children currently available as ‘Pharmacy Only’.

Nurofen for Children oral suspension, containing 20mg/ml of ibuprofen is indicated for temporary relief of pain associated with teething, toothache, earache, sore throats, headache, minor aches, sprains and strains, cold and flu and reduction in temperature. All of these pain symptoms are well characterised, usually of limited duration, and easily identified by a consumer who currently self-medicates with non-prescription analgesics.

The labelling directs consumers to seek medical advice and consult doctor if the child’s symptoms persist for more than a few days. We believe that consumers recognize that prolonged pain is a sign of something more serious as such and are able to adequately evaluate this and seek appropriate medical treatment.

The proposed pack sizes of 100ml provide for a maximum of 11 days treatment for 3 - 6 months old children however the labelling clearly states that the product is for short term use only, and with a maximum of 3 doses in 24 hours.

The easily recognisable and short-term nature of the indications for use ensures that neither medical diagnosis nor on-going medical management are required.

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| B.3. Relevant comparative data for like compounds |

The commonly known Non-Steroidal Anti-Inflammatory drugs (NSAIDs) are aspirin, ibuprofen, and naproxen, all of which are available over the counter in most countries.

There was no evidence of differences in efficacy among the NSAIDs so the attention naturally focused on their relative safety. It was estimated that at least 10 to 20 % of patients had dyspepsia while taking an NSAIDs, and 5 to 15 % of patients discontinued NSAIDs therapy because of dyspepsia10.

Although NSAIDs are generally well tolerated, the other major concern could be dose-related gastrointestinal (GI) toxicity. Ibuprofen was associated with the lowest risk in studies performed9. Naproxen and other NSAIDs including diclofenac and indomethacin were associated with risks which are obviously higher than those for ibuprofen9.

Ibuprofen has been proven more effective than paracetamol and aspirin in headache11, sore throats and fever12.

All required warnings and cautionary statements for ibuprofen are included on the package. Additional statements on the correct dosage and dosing frequency for children are highlighted on the package to increase the parents/caregivers awareness on the importance of correct ibuprofen dosing. A dosing guide is also clearly available on the package to help parents/caregivers to determine the appropriate dose for their child.

**SAFETY PROFILE OF IBUPROFEN COMPARED TO PARACETAMOL**

The safety and tolerability profile of ibuprofen as a paediatric OTC medicine is well characterised. It has a good tolerability profile and possesses a wide margin of safety and a low toxicity following overdose, compared to paracetamol. There is no estimated minimum fatal dose for ibuprofen.

Children tolerate NSAIDs well and severe adverse effects of NSAIDs in children are very rare19. The evidence of relatively low occurrence of serious adverse drug reactions (ADRs) or rare events comes from large scale practitioner or centre based studies20, 21, 22 and critical reviews of clinical trials23. The relatively low intrinsic toxicity of the drug also gives support to the view that it has a high degree of tolerability from the point of view of human toxicity24.

A systematic review and meta-analysis of the clinical safety and tolerability of ibuprofen compared with paracetamol in paediatric (children up to 18 years of age) pain and fever demonstrated that ibuprofen, paracetamol and placebo have similar tolerability and safety profiles in terms of GI symptoms, asthma and renal adverse effects25. While the study data in this review may not reflect OTC use, these results are still relevant in the context of any safety concerns relating to general ibuprofen or paracetamol treatment in children.

A total of 24 RCTs in this study examined either ibuprofen and/or paracetamol versus placebo for adverse events (AE) data. Twelve other studies meeting the selection criteria were also included for AE data. A total of 2937 systemic AEs occurred in 21,305 patients taking ibuprofen compared with 1,466 systemic AEs in 11,164 patients taking paracetamol [RR 1.03 (95% CI: 0.98-1.10)]. There was no significant difference between the two groups. Relative risk of adverse events with ibuprofen versus placebo was 1.39 (95% CI: 0.92-2.10) compared to RR 1.57 (95% CI: 0.74-3.33) for paracetamol versus placebo. Narrative analyses of AE data identified conflicting evidence regarding hepatic injury with paracetamol and group A streptococcal infections with ibuprofen or paracetamol treatment25.

The safety of ibuprofen suspension in children <2 years was demonstrated in a multicentre, open-label, prospective study at 69 US clinics that involved 424 paediatricians and enrolled 41,810 children (aged 1 month to 18 years old)20. The safety profile in children <2 years was found to be consistent with the excellent profile observed in children >2 years. Overall, ibuprofen exhibited an AE profile similar to acetaminophen in both younger and older children.

Among 30,144 children who took at least one dose of ibuprofen or acetaminophen in this study, 14,281 were younger (<2 yrs) and 15,863 were older (>2 to <12 yrs). Within both age groups, the incidence rates for specific AEs, including abdominal pain, insomnia, and hyperkinesia were rare and generally <1% for both treatments20.

A meta-analysis and qualitative review of 85 studies that directly compared ibuprofen to paracetamol (54 contained analgesic efficacy data, 35 contained antipyretic/temperature reduction data, and 66 contained safety data with some articles containing more than 1 type of data) has demonstrated similar efficacy and safety of ibuprofen and paracetamol as analgesics in adults and children26. No significant difference in AE incidence was found between drugs for paediatric patients26.

Safety of ibuprofen to support the use of the currently licensed ‘Nurofen® for Children Orange Oral suspension 2%’ was based on a report27 that includes analyses of two large-scale studies: ‘The Boston Collaborative Drug Surveillance Program (BCDSP)’, a study28 that was commissioned by Boots Healthcare International Ltd (part of Reckitt Benckiser currently), and, a practitioner-based study by Lesko and Mitchell in 199521.

The sponsored double-blind and randomised epidemiological study in the USA by Lesko et al. provides evidence on the paediatric safety of ibuprofen through a comparison of 5 and 10 mg/kg doses of ibuprofen with 12 mg/kg of acetaminophen, in 84,192 febrile children21.

The study results demonstrated that the risk of hospitalisation for GI bleeding, renal failure, or anaphylaxis was not increased following short-term use of ibuprofen in children. A total of 277 patients (0.3%) were unavailable for follow-up. Overall, 795 participants (1%) were hospitalised, primarily for infectious diseases; hospitalisation rates did not differ according to treatment group. Four children had diagnoses of acute, non-major GI bleeding (two in each ibuprofen dosage group). Among ibuprofen-treated children, the observed risk of GI bleeding [7.2 per 100,000 (95% CI: 2-18 per 100,000)] was not significantly different from the risk among acetaminophen-treated children (p=0.31). Among a number of other possibly serious adverse drug events, low white blood cell count was marginally associated with ibuprofen treatment. Because this association was observed in the setting of multiple comparisons and white blood cell counts may have been low before treatment, causation was unclear21. A separate analysis of results for the 27,605 children aged less than 2 years from this study was published in 199916. In this sub-population, the risk of hospitalisation during the 4 weeks after inclusion was low and was similar for both treatments [Absolute and relative risks for ibuprofen and paracetamol being 1.5% (95% CI: 1.3-1.6%) and 1.1% (CI: 0.9-1.3%), and, 1.4% (1.1-1.6%) and 1.0% respectively.

**IBUPROFEN VERSUS PARACETAMOL FOR PAIN**

Because of its peripheral anti-inflammatory action, ibuprofen is more effective than paracetamol for painful conditions associated with inflammation such as teething pain)23, 30. A detailed analysis of all available published data on ARs to both paracetamol and ibuprofen, specifically under OTC dosage conditions, observed that overall, paracetamol and ibuprofen have shown similar therapeutic and AEs23. It was also apparent that the reported AEs were all minor, reversible upon cessation of drug therapy, and could be managed by the patient. No deaths were recorded and no hospitalisation or major medical emergency treatment was necessary23. Some studies in which ibuprofen and paracetamol have been directly compared have indicated that ibuprofen has a longer duration of action and is more potent23, 31.

A meta-analysis and qualitative review was conducted of 85 studies that directly compared ibuprofen to acetaminophen (54 contained analgesic efficacy data, 35 contained antipyretic/temperature reduction data, and 66 contained safety data with some articles containing more than 1 type of data)26. For the most part, ibuprofen was more efficacious than acetaminophen for the treatment of pain and fever in both paediatric and adult populations. Meta-analyses on the subset of randomised clinical trial articles confirmed the qualitative results for adult and paediatric pain at 2 hours post-dose and paediatric fever at 4 hours post-dose. No significant difference in AE incidence was found between drugs for paediatric patients26.

Results obtained from another systematic review that evaluated the efficacy and safety of acetaminophen and ibuprofen in 186 children <18 years of age showed that single doses of ibuprofen (4-10 mg/kg) and acetaminophen (7-15 mg/kg) have similar efficacy for relieving moderate to severe pain, and similar safety as analgesics or antipyretics. Ibuprofen (5-10 mg/kg) was a more effective antipyretic than acetaminophen (10-15 mg/kg) at 2, 4, and 6 hours post-treatment32.

The famous PAIN (Paracetamol, Aspirin, Ibuprofen New tolerability) study, a blinded randomised comparison of the tolerability of OTC analgesics in the treatment of common types of acute pain encountered in the community, has demonstrated that low-dose ibuprofen is as effective as aspirin and paracetamol for the indications normally treated with OTC medications and is associated with the lowest risk of GI toxicity of any NSAID drug33. By contrast, even low-dose aspirin was associated with an appreciable risk of GI toxicity33.

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| B.4. Local data or special considerations relating to New Zealand |

Over the past 20 years, ibuprofen has gradually moved from prescription medicine to lower levels of classification, including ‘Pharmacy Only and ‘General Sales’ status, there is no evidence to suggest that increased consumer access has led to either an increased need for pharmacist involvement or the emergence of consumer safety issues8.

Therefore, it is not expected there would be any special considerations relating to New Zealand for this reclassification.

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| B.5. Interactions with other medicines |

Having undivided liquid dose form of ibuprofen in the ‘General Sale’ medicine classification, with the same restrictions as for divided solid dose form and liquid dose forms, will not change the risk of interactions with other medicines.

Ibuprofen is metabolised and eliminated almost completely within 24 hours of ingestion, thus reducing the potential for serious interaction. Additionally, the extensive protein binding of ibuprofen does not seem to play a significant part in drug interaction. Although various interactions have been reported with ibuprofen during its 36 years of clinical use in adults, no consistent reports of significant drug interactions relevant to medicines used routinely in the management of paediatric disorders are evident.

The principal interactions that can occur with ibuprofen are listed, in summary, as follows:

* Concurrent aspirin or other NSAIDs, taken deliberately or inadvertently, may result in an increased incidence of adverse reactions. Concomitant use of such products is therefore contraindicated with Nurofen for Children.
* NSAIDs may diminish the effect of anti-hypertensives, such as diuretics.
* There is limited evidence for enhancement of the effects of oral anti-coagulants (such as warfarin) with concomitant ibuprofen.
* Reduced clearance leading to increased plasma levels of methotrexate and lithium has been reported with ibuprofen
* Concomitant use of corticosteroids may increase the risk of adverse reactions in the gastrointestinal tract.

The labelling for Nurofen for Children includes adequate cautionary statements based on the known interactions that may occur with ibuprofen; to consult a doctor if the child is receiving any other regular treatment or medicines. However, short-term use of Nurofen for Children, at the recommended daily dose, is judged to have a low potential for interaction with other commonly administered paediatric pharmacological treatments.

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| B.6. Contraindications |

The current label indicates the following contraindications/cautions:

* Most asthmatics can take Nurofen for Children but if your child is sensitive to pain relievers, do not use this product. If you are unsure, check with your pharmacist or doctor.
* If your child is receiving any other regular treatment or medicines consult your doctor.
* In adults this product is not recommended for use by pregnant women except on a doctor’s advice. Do not use in the last three months of pregnancy.
* Do not give to babies or children who have impaired kidney function, stomach disorders or stomach ulcers, are allergic to aspirin, ibuprofen or other anti-inflammatory medicines, or are suffering dehydration.
* Do not give to babies under 3 months.
* Seek medical advice before giving to children under 1 year.

These statements will remain on the label.

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| B.7. Possible resistance |

It is not expected that short term use of ibuprofen with correct dosing will cause any resistance to develop.

In addition, ibuprofen’s safety record is significantly better than other non-steroidal anti-inflammatory agents (NSAIDs). In particular, the comparison with other NSAIDs available as non-prescription

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| B.8. Adverse events - nature, frequency etc |

Commonly known adverse effects include nausea, dyspepsia, diarrhoea, constipation, epistaxis, headache, dizziness, rash and hypertension.

In addition, drowsiness, coma, nystagmus, diplopia, hypothermia, hypotension, respiratory depression and cardiac arrest have been reported in severe cases of poisoning13.

The spontaneous reporting rates of adverse events in Australia and overseas has been low8. Ibuprofen is associated with the lowest risk of GI complications of any NSAIDs at prescribed doses6, 14. In the doses used for the maximum permitted non-prescription dose of ibuprofen (1200 mg/day), the incidence of GI events in adults is low15 and in children is low and comparable with that associated with paracetamol16.

Adverse events associated with non-prescription use of ibuprofen were evaluated in the PAIN (Paracetamol, Aspirin and Ibuprofen New Tolerability) study15. There was a total of 8677 adults patients (2900 aspirin, 2886 ibuprofen, 2888 paracetamol; 3 patients had no code label number) aged 18 to 75 involved in the study. Treatment comprised ibuprofen 1200mg/day, paracetamol 3 g/day or aspirin 3 g/day for up to 7 days. The overall tolerability of ibuprofen in this large-scale study was equivalent to that of paracetamol and better than that of aspirin. Based on the result from the PAIN study, ibuprofen can be recommended first, because of the poor tolerability of aspirin and the potential risk of paracetamol overdose. Below is summarized table of frequency of adverse events in the PAIN study (% patients affected)15.

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| --- | --- | --- | --- |
| **Adverse events** | **Aspirin** | **Ibuprofen** | **Paracetamol** |
| All significant events | 18.7 | 13.7 | 14.6 |
| Severe events | 4.8 | 3.5 | 3.2 |
| Moderate events | 12.2 | 8.5 | 10.2 |
| Events leading to premature discontinuation | 7.6 | 8.1 | 6.1 |
| Events leading to additional consultation | 4.9 | 3.5 | 3.5 |

Below is the number of NZ cases for both adults and children reported to the Joint Adverse Event Notification System (JAEN) for the period from 01 January 2000 to 30 January 2013. JEANS contains information from reports of adverse events that the Therapeutic Goods Administration (TGA) and Centre for Adverse Reactions Monitoring (CARM) have received in relation to medicines used in Australia and New Zealand17.

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| Number of reports/cases (NZ)Multiple adverse events have been reported for some patients | 138 |
| Number of cases with a single suspected medicine – ibuprofen (NZ)(The TGA or CARM think there is a possibility that the medicine caused the adverse event) | 86(18 cases for children 1-12 years) |

Given the above safety data and warning statements on the label, adverse effects with OTC short-term use ibuprofen are rare. Ibuprofen should not be considered as just another NSAIDs but rather a safe, proven analgesic/antipyretic which is internationally acknowledged for self-medication.

Adverse event data for Nurofen for Children has been pooled for the number of adverse events reported from New Zealand. For the period of 2006 up to 2013 a total of one adverse event has been reported and this was considered non serious. The adverse event concerned a child who vomited 12 hours following dosing with Nurofen for Children (unspecified bottle size or flavour), the child had previously been given the product over the previous 18 months with no problems. The mother took the product to the USA where it was over 35°C. Her daughter was also taking antibiotics for a throat infection, and was given Nurofen for Children for her fever and teething pain. The adverse event ‘nausea’ was attributed to Nurofen for Children and no distinction has been made between the 100ml bottle and the 200ml bottle. Since the launch of Nurofen for Children Suspensions product the frequency of adverse event reporting in New Zealand has remained significantly low.

Over the last six years the profile of possible adverse reactions reported to ibuprofen has not changed significantly and is consistent with the safety profile for ibuprofen that has been well characterised in over 21 years’ use as an OTC medicine.

Annual Production Sales Volumes and Reported Adverse Events for Nurofen for Children suspensions in New Zealand as below:

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| **Year** | **Production Sales Volumes - Packs in thousands** | **Frequency of Adverse Events Reported to Children** |
| **Nurofen for Children Suspension** | **All Adverse Events (Number of patients)** | **All Serious Adverse Events (Number of****patients)** |
| 2006/2009 |  62,952 | 1 (1) | 0 (0) |
| 2009/2013 | 224,382 | 0 (0) | 0 (0) |
| **Total** | **287,334** | **1 (1)** | **0 (0)** |

Since 1st October 2006 over 28.5 million units of Nurofen for Children have been sold in the UK as a General Sale medicine and in this time 220 adverse events have been reported to Reckitt Benckiser in the UK (information taken from Reckitt Benckiser’s pharmacovigilance database).

Production Sales Volumes for Nurofen for Children Suspension in the UK as below (information taken from Reckitt Benckiser’s PSURs):

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| **Period** | **Nurofen for Children Suspension (Orange)** | **Nurofen for Children Suspension (Strawberry)** |
| 1/10/06 – 30/9/07 | 1,981,000 | 1,859,000 |
| 1/10/07 – 30/9/08 | 1,944,401 | 1,794,870 |
| 1/10/08 – 28/2/11 | 10,529,583 |
| 1/3/11 – 29/2/12 | 5,221,965 |
| 1/3/12 – 30/4/13 | 5,305,779 |
| **TOTAL** | **28,636,598** |

**SAFETY PROFILE AND CONSIDERATIONS**

The safety and tolerability profile of ibuprofen as a paediatric OTC medicine is well characterised. It has a good tolerability profile and possesses a wide margin of safety and a low toxicity following overdose. There is no estimated minimum fatal dose for ibuprofen.

Ibuprofen is clinically proven to be well tolerated in children as young as 3 months old, with a safety profile at least as good as paracetamol when used as an analgesic and antipyretic in this patient population21. Nurofen® for Children has been shown to provide a rapid [as early as 15 minutes after dosing34] onset of antipyresis and compared with paracetamol has been demonstrated to be more effective [greater reduction of temperature32, 35, 36, and longer lasting (up to 8 hours)12, 32, 35, 38. On a dose-per-dose basis, ibuprofen has been found to be more effective than paracetamol in reducing high temperatures (>39.2o)34, 39.

The safety and tolerability profile of over-the-counter ibuprofen in adults and children is well characterised and summarised below.

***Bronchospasm / NSAID-induced asthma****:* The prevalence of bronchospasm, which presents as bronchial asthma in association with ibuprofen, is very rare. This is supported by Lesko and Mitchell (1995)21 a large-scale, randomised, double-blind, population-based study, in children aged one month to 12 years, that identified 44 cases of hospitalisation associated with asthma in over 55,785 children who had received ibuprofen (5 or 10 mg/kg). Whereas there were 24 cases reported to paracetamol in 28,130 children who received paracetamol (12 mg/kg).The results were therefore comparable for both treatment groups.

However, there is a subset of asthma sufferers who have a known syndrome called aspirin sensitive asthma (ASA). ASA is thought to be related to cyclooxygenase (COX) inhibition; therefore, it is important that aspirin-sensitive asthmatics avoid all NSAIDs, including ibuprofen. Such individuals usually have associated conditions, including:

* Significant nasal polyps
* Sensitivity to all NSAIDs
* Allergic rhinitis, often recognised by the patient after taking an NSAID
* Sinusitis, often with X-ray changes, such as opacity of the sinuses
* Persistent, severe asthma requiring management with corticosteroids
* Chronic urticaria
* Dietary sensitivities

Accordingly, Nurofen for Children is contraindicated in individuals with known hypersensitivity to ibuprofen or other pain relievers. The product is also contraindicated in individuals who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angiodema or urticaria) in response to aspirin or other NSAIDs.

Ibuprofen need not be withheld from all asthmatic patients, especially the low risk groups who have mild extrinsic (allergic) asthma and no nasal polyps, and those who have previously been shown to tolerate it. The majority of patients with asthma can take ibuprofen with no adverse sequelae.

***Gastrointestinal effects***: The incidence of gastrointestinal adverse events with orally administered ibuprofen is related to the dose taken, and doses of ≤ 1200mg daily are associated with much lower incidence than prescription doses. In a comprehensive review of clinical studies comparing ibuprofen and paracetamol when taken at recommended OTC doses, no reports of melaena or haemorrhage from the gastrointestinal tract were found with ibuprofen in any of the studies23.

The incidence of adverse events, including GI adverse events, in patients receiving ibuprofen is low and similar to that with paracetamol at OTC doses23, 40. The number of gastrointestinal events experienced with ibuprofen were lower than those associated with paracetamol15. Rainsford23 conducted a meta-analysis to the incidence of side-effects of ibuprofen, paracetamol and aspirin in controlled clinical trials in which the drugs were taken at recommended OTC dosages. The analysis was performed on published data. The studies were selected according to inclusion and exclusion criteria that would allow analysis of the adverse effects attributable to ibuprofen and paracetamol without confounding variables such as the intake of other drugs. Reports were included for treatment periods greater than 7-10 days (the recommended OTC dosage duration proposed by the author), so that longer-term effects could also be examined. On examination of the gastrointestinal adverse events Rainsford concluded that: ‘the incidence of gastrointestinal adverse events was not statistically significantly different between ibuprofen and paracetamol, and no clinically significant events such as bleeding or melaena were seen with ibuprofen’.

In the published literature, when individual NSAIDs have been compared, ibuprofen has been consistently associated with the lowest risk of GI complications6, 42. The risk of gastrointestinal adverse events with Nurofen for Children is very low, when used for short periods at the recommended dose.

Nurofen for Children is contraindicated in children with stomach disorders or stomach ulcers and is stated on the labelling.

***Renal effects****:* Ibuprofen at OTC doses in adults has not been shown to have any significant effects on the renal system. A few reports have shown that renal adverse events are dose-related; however, these usually occur in patients with pre-existing disease or other contributing factors44.

With regards to a paediatric population, renal function was monitored in a subgroup of children (285 of 27,065) who were admitted to hospital while participating in a randomised double-blind trial of 5 or 10 mg/kg of ibuprofen or paracetamol 12 mg/kg for the treatment of febrile illness21. There was no difference between the treatments in blood urea nitrogen levels, serum creatinine concentrations or the incidence of serum creatinine concentrations > 62 micromol/l. The authors concluded these data suggest that the short-term risk of less severe renal impairment associated with short-term use of ibuprofen in children is small and not significantly different from that with paracetamol. There was also no difference between ibuprofen and paracetamol in the risk of admission for acute renal failure43 demonstrating that the short-term use of ibuprofen does not increase the risk of renal impairment relative to that of paracetamol.

Nurofen for Children is contraindicated in children with impaired kidney function and is stated on the labelling.

***Other contraindications and special precautions for use****:* Nurofen for Children is contraindicated in patients suffering from dehydration.

Safety in the context of a General Sale classification relates principally to any issues which could arise out of the purchase and use of a medicine without the benefit of any healthcare professional advice. In the particular case of ibuprofen paediatric suspension, the principle of General Sale supply has already been established since 2002 within the UK.

Since the General Sale launch of Nurofen for Children Singles in the UK in May 2002, no adverse events have been specifically reported to this product, as part of the post marketing surveillance, although approximately 4.4 million packs have been manufactured and delivered to the market.

It should be noted that the packaging for Nurofen for Children suspension has a tamper evident seal and a child resistant cap making it more difficult for large quantities to be swallowed accidentally by a child. Furthermore the product has a unique dosing syringe which requires a special bung in the bottle neck. This makes accidental use by a young child even more difficult. When this is considered in respect to the known low toxicity of ibuprofen in overdose the 100 ml bottle packs can be considered as a low safety risk.

The labelling carries full information for the safe use of the product.

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| B.9. Potential for abuse or misuse |

Ibuprofen has been readily available in many countries for several years as an Over-the-Counter (OTC) product and has a very low to absent potential for abuse or misuse as supported by its General Sales status8.

The proposed reclassification of liquid form of ibuprofen for children to a ‘General Sale’ medicine is not expected to increase the potential for abuse or misuse as this is for short-term emergency treatment only. The product is also packed in child-resistant packaging and a plastic syringe is also included in the package for parents/caregivers to administer the correct dose. Pack size limited to 100ml in manufacturer’s original packaging will also ensure product is for short term emergency treatment only. It is also clearly stated on a pack to seek medical advice before giving to children under 1 year, therefore reinforces informed use by parents/caregivers.

Ibuprofen has no obvious potential for drug abuse and no published case report of intentional abuse with single-ingredient ibuprofen formulation was identified in the literature. Ibuprofen does not possess significant central nervous system stimulatory effect or strongly sedating effect - thus making it a poor candidate for recreational drug abuse. The potential for drug abuse with Nurofen for Children ibuprofen suspension is therefore considered to be highly remote.

The key to further minimizing potential risks to the consumer is to continue to find better ways to educate (detailed information can be provided on website – [www.nurofenforchildren.co.nz](http://www.nurofenforchildren.co.nz)), encourage consumers to read, comprehend and comply with current label warnings and directions for use.

**OVERDOSE**

The safety and efficacy of ibuprofen is strongly established, and the risk of severe toxicity in case of intentional overdose is minimal46, 47. It has proved to be a better alternative to many other common analgesics for the relief of pain arising in a variety of clinical conditions. Ibuprofen has a low toxicity in overdose. The toxic effects of ibuprofen are related to the pharmacological action i.e. prostaglandin synthesis and the accumulation of the acidic metabolites, rather than additional pathophysiological activity as seen with aspirin and paracetamol. Ingested doses do not correlate well with clinical effect; however, in general, at doses below 100 mg/kg, patients are asymptomatic, at doses in the range of 100 – 400 mg/kg patients can experience mild to moderate symptoms and at doses greater than 400 mg/kg symptoms tend to be moderate to severe and are likely to be serious48.

The most frequently reported symptoms are nausea, vomiting and abdominal pain. Other reported symptoms include: headaches, drowsiness, diarrhoea, coma, convulsions, gastrointestinal haemorrhage, cytolytic and cholestatic hepatic attack, acute renal insufficiency, respiratory depression and metabolic acidosis46, 48.

There is no specific antidote for ibuprofen overdose therefore management should be symptomatic and supportive. The administration of activated charcoal (1 g/kg) within 1 hour of ingestion is recommended by the National Poisons Information Service (NPIS) in the UK after a potentially toxic dose has been taken. For each individual patient the benefit: risk of administering activated charcoal should be assessed as this treatment carries its own inherent risk which can outweigh the risks associated with ibuprofen alone overdose. All patients should be observed for at least four hours following on from ingestion.

Doses of the order of 100 times the single therapeutic dose (933, 670 and 560 mg/kg) have been associated with recovery following symptomatic treatment in three children29. Reversible renal insufficiency was reported after 640 mg/kg ibuprofen and plasma concentrations of 1,750 μmol/l, 4 hours after dosing45. Of 62,800 cases of intoxication by analgesics reported to American Anti-Poison Centers in 1984, 4,800 concerned children, of whom 1,000 were intoxicated by ibuprofen. There were no fatalities in children with ibuprofen, paracetamol or aspirin41.

Ibuprofen has a wide therapeutic index. The maximum recommended single therapeutic dose for ibuprofen in children is 10 mg/kg and the toxic dose is 400 mg/kg; therefore, using the lowest estimate of the toxic dose, its therapeutic index is 40. This large safety margin is particularly relevant to young children, in whom metabolic systems are still developing and may be influenced by a variety of factors.

OTC ibuprofen is probably the least toxic of NSAIDs, being rarely associated with deaths from accidental or deliberate ingestion or with serious adverse reactions (AR). Indeed, it has been described as "the mildest NSAIDs with the fewest side effects which has been in clinical use for a long time"24, 37. Following the encouraging results from the PAIN study, the French Medicines Agency recommended ibuprofen as a "drug for first intention treatment in acute situations" in January 200133.

In summary, extensive use of ibuprofen from 1969 onwards has shown that ibuprofen possesses a wide margin of safety and a low toxicity following overdose. There is no estimated minimum fatal dose for ibuprofen.

It should be noted that the packaging for Nurofen for Children suspension has a child resistant cap making it more difficult for large quantities to be swallowed accidentally.

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