ADVIL IBUPROFEN SUGAR FREE 100MG/5ML ORAL SUSPENSION

PL 00165/0366

UKPAR

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ADVIL IBUPROFEN SUGAR FREE 100MG/5ML ORAL SUSPENSION

PL 00165/0366

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency granted Whitehall Laboratories Limited a Marketing Authorisation (licence) for the medicinal product Advil Ibuprofen Sugar Free 100mg/5ml Oral Suspension (PL 00165/0366) which is a duplicate application of the currently approved product, Children's Advil Sugar Free Suspension (PL 00165/0143) licensed to the same Marketing Authorisation holder. This is a pharmacy-only medicine (P) and is used for the treatment of mild to moderate pain such as sore throat, earache, headache, toothache, teething pain, minor aches and sprains, and for the reduction of fever including post immunisation pyrexia.

Advil Ibuprofen Sugar Free 100mg/5ml Oral Suspension contain the active ingredient ibuprofen, which is a Non-Steroidal Anti-inflammatory Drug (NSAID) that works by relieving pain, and reducing inflammation, swelling and fever.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Advil Ibuprofen Sugar Free 100mg/5ml Oral Suspension outweigh the risks; hence a Marketing Authorisation has been granted.

ADVIL IBUPROFEN SUGAR FREE 100MG/5ML ORAL SUSPENSION

PL 00165/0366

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Advil Ibuprofen Sugar Free 100mg/5ml Oral Suspension (PL 00165/0366) on 27th February 2007. The product is a pharmacy-only medicine.

Advil Ibuprofen Sugar Free 100mg/5ml Oral Suspension was submitted as an abridged application according to Article 10 of Directive 2001/83/EC, as amended. This is a duplicate application of the currently approved Children's Advil Sugar Free Suspension (PL 00165/0143), and has been shown to have the same efficacy and safety as that of the reference product Nurofen Tablets 200mg (Crookes Healthcare Ltd). The reference product has been have been authorised in the EU since February 1971 and so the 10-year period of data exclusivity has expired.

The product contains the active ingredient ibuprofen. Ibuprofen is a non-steroidal anti-inflammatory agent that has demonstrated its efficacy by inhibition of prostaglandins synthesis. Ibuprofen possesses analgesic and antipyretic properties and is used to reduce inflammatory pain, swellings and fever.

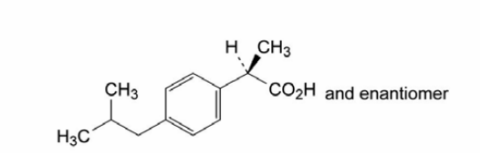
Advil Ibuprofen Sugar Free 100mg/5ml Oral Suspension is indicated for the relief of mild to moderate pain including rheumatic or muscular pain, sore throat, earache, headache, toothache, teething pain, feverishness and symptoms of colds and influenza; also for the reduction of post immunisation pyrexia.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Ibuprofen

INN: Ibuprofen
Chemical Name: (2RS)-2-[4-(2-Methylpropyl)phenyl]propanoic acid
Structure:



Molecular formula: $C_{13}H_{18}O_2$
Molecular weight: 206.3

Physical form: White odourless crystalline powder or colourless crystals

Chirality: Racemic

All aspects of the manufacture, in-process controls, validation and active substance specification are covered by a certificate of suitability for the active substance manufacturer, with the additional in-house test for particle size.

Active ibuprofen is stored in lock-rim fibre drums. Suitable specifications have been provided for all packaging and the primary packaging has been shown to be suitable for contact with food.

Suitable stability data have been generated supporting a retest period of three years, when stored in lock-rim fibre drums.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely glycerol, xanthan gum, maltitol liquid, sodium benzoate, disodium edetate, polysorbate 80, citric acid anhydrous, saccharin sodium, acesulfame potassium, strawberry flavour 11407-33, banana flavour 10995-36 and purified water. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeial monograph, with the exception of strawberry flavour 11407-33 and banana flavour 10995-36 which comply with in-house specifications; this is acceptable. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contains material of animal or human origin.
There were no novel excipients used and no overages.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on three pilot-scale and three full-scale batches. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

Product is packaged in 100ml glass bottles with a child-resistant polypropylene cap with a natural low-density polyethylene liner.
Specifications and certificates of analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, with no special precautions for storage, which is satisfactory.

Conclusion

It is recommended that a Marketing Authorisation is granted for this application.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for an application of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION

This is an abridged hybrid application for ibuprofen suspension (100mg of ibuprofen per 5 ml) for paediatric use and it is supported by the Company-sponsored clinical trials.

Ibuprofen [2-(4- isobutylphenyl) propionic acid] inhibits prostaglandin synthesis by competitive inhibition of the two isomers of cyclooxygenase, COX-1, and COX-2. It is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and antipyretic properties.

Ibuprofen was licensed in the UK as a Prescription Only Medicine (POM) product in 1969 and its licence was extended to Over The Counter (OTC) sales in 1986. Currently, in the UK, there are over 250 products containing ibuprofen in different formulations and dosage strengths.

The Applicant claims that the application has been made according to Article 10 of Directive 2001/83/EC, as amended.

Numerous proprietary and generic oral suspensions of ibuprofen are already licensed. There are two Marketing Authorisations (MAs) granted in the UK to cover the use of ibuprofen in infants from the age of 6 months (Junior Ibuprofen Suspension, PL 16028/0034 and Nurofen for Children Sugar Free, PL 00327/0085).

2. INDICATIONS

The Applicant proposes the following:

For the relief of mild to moderate pain including rheumatic or muscular pain, sore throat, earache, headache, toothache, teething pain, feverishness and symptoms of colds and influenza. Also used for the reduction of post immunisation pyrexia.

The proposed indications are in principle similar to the indications for other ibuprofen suspensions for children.

2.1.1 LEGAL STATUS

The legal status is ‘Pharmacy’ in line with the approved application PL 00165/0143.

3. DOSE & DOSE SCHEDULE

The Applicant proposes the following:

Generally, the daily dosage is 20mg per kg of body weight in divided doses.

Infants 6 months to 1 year: 2.5ml 3 times in 24 hours
Children 1 to 2 years: 2.5ml 3-4 times in 24 hours
Children 3 to 7 years: 5ml 3-4 times in 24 hours
Children 8 to 12 years: 10ml 3-4 times in 24 hours

For post immunisation pyrexia: one 2.5ml spoonful followed by one further 2.5ml spoonful 6 hours later if necessary. If the fever is not reduced, consult your doctor.

Not recommended for children under 6 months of age.
Not recommended for more than 3 days without consulting a doctor.

4. CLINICAL PHARMACOLOGY
4.1 PHARMACODYNAMICS

Ibuprofen has similar pharmacokinetics and pharmacodynamic in adults and children, and plasma ibuprofen concentrations of 6-10μg/ml in children should be consistent with an analgesic effect.
Ibuprofen suspension in a dose of 5mg/kg of body weight produces plasma concentrations above this threshold within 30 minute after dosing in febrile children.

4.2 PHARMACOKINETICS

Ibuprofen is rapidly and almost completely absorbed.
In general, therapeutic regimens in paediatric patients are based on the extrapolation of pharmacokinetic data from adults and a literature review of relevant papers is provided with this application.
The pharmacokinetics of ibuprofen are not affected by a dose between 5 and 10mg/kg or age between 2 and 10 years old.
The effect of age on ibuprofen pharmacokinetics in infants and children aged 3 months to 10 years demonstrated that age did not significantly influence the rate of absorption, plasma concentration or elimination.
In adults, the plasma half-life of ibuprofen is 1.5-2 hours. In febrile children the plasma half-life is 1.65 and 1.48 hours for ibuprofen 5mg/kg and 10mg/kg, respectively.

4.3. BIOEQUIVALENCE

One study has been submitted investigating bioavailability of Children's Advil Sugar Free Suspension and Nurofen 200mg tablets

4.3.1 **Study 068-xx**

It was a crossover, open-label study in healthy, male subjects. The primary objective of this study was to compare the rate and extent of ibuprofen absorption from Sugar Free Advil Suspension (European), 100 mg/5 ml, to Nurofen 200 mg Tablets. As a secondary objective, the study also evaluated the pharmacokinetic profile of Children's Advil Suspension (US) 100 mg/5 ml.

The pharmacokinetic properties were assessed by measuring serial plasma ibuprofen concentrations after administration of each formulation. The following parameters were calculated: AUC (0-t), AUC (0-inf), K_{el}, $T_{1/2el}$, C_{max} and T_{max}. A parametric (normal-theory) general linear model was applied to each of the above parameters. In addition, the logarithmic transformations (LN) of AUC (0-inf), AUC (0-t), and Cmax were analysed with the same model. The analysis of variance (ANOVA) model included the following factors: treatment, sequence, subject within sequence, period and carry-over effect. The sequence effect was tested using the subject within sequence mean square and all other main effects were tested using the residual error

(Type III error mean square). 90% confidence intervals for the ratio of least-squares (LS) means for Sugar Free Suspension (European) versus Nurofen 200 mg Tablets and Sugar Free Advil Suspension (European) versus Children's Advil Suspension (US) were calculated for the parameters AUC (0-t), AUC (0-inf), and C_{max} using both untransformed and LN-transformed data.

The overall mean pharmacokinetic parameters and statistical comparisons are summarised in Table 1, 2, and 3.

Table 1. Ibuprofen Pharmacokinetic Parameters [Arithmetic mean (SD)]

Ibuprofen Pharmacokinetic Parameters	Sugar Free Advil Suspension (European)	Children's Advil Suspension (US)	Nurofen 200 mg Tablets
C_{max} (µg/ml)	39.9 (5.2)	40.0 (7.2)	36.4 (5.9)
T_{max} (hr)	0.67 (0.19)	0.63 (0.61)	1.51 (0.66)
AUC (0-t) µg*hr/ml)	116.9 (31.1)	106.0 (28.8)	119.6 (31.8)
AUC (0-inf)(µg*hr/ml)	118.4 (31.7)	107.5 (29.4)	121.1 (32.7)
$T_{1/2el}$ (hr)	2.10 (0.32)	2.11 (0.30)	2.04 (0.34)
K_{el} (1/hr)	0.338 (0.049)	0.335 (0.042)	0.348 (0.055)
LN (C_{max})	3.68 (0.14)	3.66 (0.20)	3.58 (0.16)
LN [AUC (0-t)]	4.73 (0.24)	4.63 (0.24)	4.76 (0.24)
LN [AUC (0-inf)]	4.74 (0.24)	4.65 (0.24)	4.77 (0.24)

Table 2. Statistical Comparisons Sugar Free Advil Suspension (European) versus Nurofen 200 mg Tablets

Ibuprofen Pharmacokinetic Parameters	Mean ratio % EU susp. vs Nurofen tbs	90% confidence intervals EU susp. vs Nurofen tbs
LN (C_{max})	114.1	103.7-125.6
LN [AUC (0-t)	99.3	96.4-102.3
LN [AUC (0-inf)	99.4	96.5- 102.3

Table 3 Statistical Comparisons Sugar Free Advil Suspension (European) versus Children's Advil Suspension (US)

Ibuprofen Pharmacokinetic Parameters	Mean ratio % EU susp. vs US susp	90% confidence intervals EU susp. vs US susp
LN (C_{max})	102.1	92.8-112.4
LN [AUC (0-t)	111.7	108.4-115.0
LN [AUC (0-inf)	111.5	108.3-114.8

The extent of Ibuprofen absorption from 20 ml (100 mg/5 ml or 400 mg) Children's Advil Sugar Free Suspension (European) to that of 2 x 200 mg Nurofen Tablets was very similar with less than 2% difference in LS (least-squares) mean AUC between the treatments. LS mean C_{max} was approximately 14% higher for the Children's Advil

Sugar Free Suspension. As expected, LS mean T_{max} was delayed for the tablet formulation (1.6 hours compared to 0.63 hours for the suspension), due to the time required for disintegration and dissolution of the tablet. The formulations met the requirement for bioequivalence with respect to AUC, since the 90% confidence intervals for the least squares mean ratios for the LN-transformed parameters (AUC (0-t), and AUC (0-inf) fell within the 80-125% limits. However, LN (C_{max}) fell just outside the limits (mean ratio 114.1, 90% CI: 103.7 to 125.6). LS mean half-life values were practically identical between the two treatments (2.1 hours).

A secondary objective of the study was to compare 400 mg Children's Advil Sugar Free Suspension (European) to 400 mg Children's Advil Suspension (US). The two suspension formulations met the requirement for bioequivalence. The LS (least-squares) mean C_{max} values were nearly identical (less than 2% difference). The mean AUC values were approximately 11% higher for the Sugar Free EU formulation. LS mean half-life values were practically identical (2.1 hours).

5. EFFICACY

The Applicant submitted several efficacy studies assessing ibuprofen suspension 100mg/5ml, including the US formulation of Children's Advil Suspension, manufactured by Whitehall Laboratories.
These trials were carried out according to Good Clinical Practice guidelines.

Additionally, various ibuprofen studies from the literature have been referred to in the Clinical Expert Report.

5.1 Fever

Two randomised studies using the US formulation of Children's Advil Suspension were submitted.

5.1.1 Study AF 95-xx

It was a randomised, single-dose, double-blind study to compare the antipyretic efficacy and safety of Children’s Advil Suspension 100mg/5ml and paracetamol suspension 160mg/5ml in children aged 6 months to 11 years. Each child received either 7.5mg/kg of Children’s Advil Suspension or 10-15mg/kg of Children’s Tylenol Suspension.

The mean reductions in temperature in the ibuprofen group were significantly greater than in the paracetamol group from one hour through to the end of the study.
The study concluded that ibuprofen was superior to paracetamol suspension in treating fever in children.

5.1.2 Study AF 95-xy

It was a randomised, single-dose, single-blind study to compare the antipyretic efficacy of single doses of ibuprofen 50mg chewable tablets and ibuprofen suspension 20mg/ml in children aged 2 to11 years.

The study concluded that ibuprofen chewable tablets and ibuprofen suspension provided comparable antipyretic efficacy when administered at a dose of 7.5mg/kg.

5.1.3 Kauffman R. E. et al (1992)
It was a randomised, double-blind, single dose study to compare the antipyretic action of ibuprofen (Brufen Syrup), paracetamol and placebo in 38 children aged 2-12 years with an oral temperature ≥ 38.3ºC.

Ibuprofen was administered in a single dose of 7.5 or 10mg/kg and paracetamol in a single dose of 10mg/kg.

Oral temperature was measured twice during the hour before the study medication was administered, 30 minutes after dosing, and at 1, 2, 3, 4, 5, 6 and 8 hours after dosing.

All three active treatments produced significant antipyresis compared with placebo. Ibuprofen demonstrated a greater temperature decrease and longer duration of antipyresis than paracetamol when the two drugs were administered at equivalent doses. There was no significant difference in temperature at any time after dosing between 7.5 and 10mg/kg of ibuprofen.

The study concluded that ibuprofen was a potent antipyretic agent.

5.1.4 Czaykowski D. et al (1994)
It was a randomised, double-blind, single dose study to assess the efficacy of ibuprofen (Brufen Syrup) compared with paracetamol in 118 children aged 6 months to 8 years with a fever ≥ 101ºF (oral) or > 102ºF (rectal).

Ibuprofen was administered in a single oral dose of 5mg/kg if rectal temperature was ≤ 102.5ºF or 10mg/kg if temperature was > 102ºF.
The dose of paracetamol was 10-15mg/kg.
Temperatures were taken hourly up to 6 hours after dosing.

The study concluded that ibuprofen was superior to paracetamol in the rate and the decrease of temperature.

5.1.5 Walson P. D. et al (1992)
It was a randomised, double-blind, multiple dose study to compare the antipyretic efficacy of ibuprofen (Brufen Syrup) at three dose levels with paracetamol in 64 children aged 6 months to 12 years (oral or rectal temperature of 38ºC to 40.5ºC).

Ibuprofen was administered at doses of 2.5 mg/kg (15 children), 5 mg/kg (15 children) and 10mg/kg (15 children); paracetamol was administered at a dose of 15mg/kg. Both treatments were administered every 6 hours for 24 to 48 hours. Oral or rectal temperatures were recorded before dosing, hourly for the first 6 hours after dosing, 3 hourly for the next 30 hours and 6 hourly for the final 12 hours.

The results are summarised in Table 5.

Table 5: Fever Reduction and Length of Treatment

Fever Reduction and Length of Treatment*								
	0-6 h		0-12 h		0-24 h		0-48 h	
Treatment	Mean % Decrease in Temperature	AUC	Mean % Decrease in Temperature	AUC	Mean % Decrease in Temperature	AUC	Mean % Decrease in Temperature	AUC
Ibuprofen 2.5 mg/kg	34.5	261 +	73.1	696	79.6	1721	88.6	3810
5 mg/kg	38.9	297	58.2	689 ‡	62.9	1572 ‡	70.5	3286
10mg/kg	73.2§	385	84.0	929	67.8	1995	80.0	3933
Paracetamol, 15mg/kg	65.9	377	94.3	938	87.5	2100	89.4	4400
F	2.73	3.24	1.50	2.60	1.02	2.43	0.67	1.98
P	.05	.03	.22	.06	.39	.07	.58	.13

* AUC indicates area under the curve
+ p<.05 compared with paracetamol and 10-mg/kg ibuprofen therapy
‡ p<.05 compared with paracetamol
§ p<.05 compared with 2.5-mg/kg and 5.0-mg/kg ibuprofen therapy

Ibuprofen 10mg/kg was comparable to paracetamol 15mg/kg for the rate of temperature reduction and the peak temperature reduction; both were better than the two lower ibuprofen doses over the first 6 hours. After the second dose, all four treatments were comparable.

The study concluded that ibuprofen 10mg/kg was comparable in efficacy to paracetamol 15mg/kg.

5.2 Pain in children

5.2.1 Dental pain - Study 390/xxy

Two single centre studies with identical protocols were combined. These were randomised, double blind, single dose studies to assess the efficacy and safety of Children's Advil Suspension compared with paracetamol suspension and placebo in children aged 8 to 14 years with dental pain.

Ibuprofen-treated children exhibited both a significantly higher pain relief and pain intensity difference then placebo treated children from one through four hours after dosing

5.2.2 Otitis media (earache) - Study WM-xxz

It was a randomised, double-blind, single dose study to evaluate the efficacy and safety of Children's Advil Ibuprofen Suspension 10mg/kg when compared to placebo in children aged 5 to 12 years with acute earache due to otitis media.

The summary measurements over the first six hours were not significantly different between groups, likely due to the large number of dropouts by the end of the trial.

The study concluded that a single dose of ibuprofen suspension 10mg/kg was an effective analgesic for the relief of earache in children up to 12 years of age.

5.2.3 Sore throat pain - Study WM-xyx

It was a double-blind, single dose study to compare the efficacy and safety of Children's Advil Suspension with paracetamol and placebo in the relief of sore throat pain.

Children were randomly allocated to the following treatment groups:
- Children's Advil Ibuprofen Suspension 10mg/kg
- paracetamol 15mg/kg
- placebo

The primary criteria for evaluation were: tonsillo-pharyngitis assessment and sore throat pain ratings.

Over the first two hours the ibuprofen group had a significantly greater pain relief as assessed by parents, compared to placebo. At two hours the treating paediatrician also rated pain reduction significantly greater in ibuprofen-treated children, compared against placebo. At six hours parents gave a significantly higher global rating to ibuprofen treatment than placebo. Paracetamol treatment was more frequently distinguished from placebo than was ibuprofen, however there were no significant differences between the two active treatments. The absolute magnitude of the observed differences in the parent and paediatrician ratings between ibuprofen- and paracetamol-treated children was small and no clinically meaningful difference between the two analgesics was observed.

5.2.4 Immunisation (Diez-Domingo et al., 1998)

It was a randomised, open study in 256 children aged 3, 5 and 7 months who received vaccination (diphtheria-tetanus-pertussis and oral polio).

Children received ibuprofen either prophylactically (20mg/kg in three divided doses over 24 hours, with the first dose given at vaccination, N=125) or symptomatically (7.5mg/kg when untoward symptoms occurred, N=131). Adverse effects (including fever) were recorded by parents. Children receiving prophylactic ibuprofen experienced mild injection site pain significantly less frequently following the first two vaccine doses, compared to those treated symptomatically. Prophylactic ibuprofen-treated children were significantly less likely to have injection site induration than those treated symptomatically (Table 8).

Table 8. Effect of Ibuprofen on Local Adverse Reactions Post Immunisation

Local Reactions	DTP Dose 1		DTP Dose 2		DTP Dose 3		DTP Doses 1-3	
	Prophylaxis (n=125)	Treatment (n=131)	Prophylaxis (n=117)	Treatment (n=118)	Prophylaxis (n=114)	Treatment (n=114)	Prophylaxis (n=356)	Treatment (n=363)
Redness	41.6	44.3	41.9	38.1	41.2	46.5	42.1	43.0
Edema	28.4	32.8	20.5	19.5	28.9	34.2	24.7	28.9
Induration	37.6	44.3	35.9	41.5	33.3	47.4	35.7	44.4*
Pain								
Mild	30.3	43.4*	36.5	43.6*	39.1	45.6	37.5	41.9
Moderate	3.3	8.5	1.7	10.4	10.9	14.9	5.2	11.2
Severe	2.5	5.4	5.1	2.6	5.5	4.4	4.3	4.2

The levels of pain were defined as follows: mild = tenderness when the vaccination site was touched;
moderate = pain on movement of the vaccinated leg; severe = refusal by the child to move the vaccinated leg.
* $P<0.05$ versus the prophylaxis group.

Children treated prophylactically also showed significantly less frequent systemic side effects than those treated only after side effects occurred: prolonged crying, unusual crying, and drowsiness following the first vaccination; fretfulness following vaccine dose 3; and unusual crying averaged over all three immunisations. There was no difference between the two treatment regimens in the frequency of elevated rectal temperature.

5.2.5 Migraine (Hamalainer M.L. et al., 1997)

It was a randomised double blind, single dose study to assess the efficacy of ibuprofen and paracetamol compared with placebo in the acute treatment of migraine in children aged 4 to 16 years.

Eighty-eight children were randomised to receive either ibuprofen 10mg/kg or paracetamol 15mg/kg, or placebo.

Three migraine attacks were treated in random order. Headache severity was rated on either a 5 point scale or 100mm visual analogue scale (VAS) at 30 minutes and then hourly for up to 5 hours after treatment administration. Primary analysis included 66 children and the intent-to-treat analysis included 85 children. Reduction in severe or moderate headache after 2 hours by at least two points was reached twice as often with paracetamol and three times as often with ibuprofen compared to placebo. Ibuprofen was twice as likely as paracetamol to abort migraine within 2 hours.

There were no significant differences between ibuprofen and paracetamol in the intent-to-treat population.

5.2.6 Postoperative tonsillectomy (St Charles, C. S. et al., 1997)

It was a randomised, single dose open study to compare the analgesic efficacy of ibuprofen with that of paracetamol with codeine in 110 children aged 16 months to 14 years undergoing tonsillectomy.

Fifty-five children received ibuprofen (Pediaprofen) 5 or 10mg/kg (for temperatures 37ºC - 39.2ºC, and >39ºC, respectively) and 55 received paracetamol 15mg/kg with codeine 1mg/kg. Children received approximately 4 doses during the first postoperative day. Main outcome measures were assessment of postoperative bleeding, pain and pain relief, nausea, emesis and temperature.

Pain was evaluated on the pain-intensity scale by nursing staff.

The average pain-intensity rating for the ibuprofen group was 1.9 compared with 2.0 for the paracetamol/codeine group. No difference was found between the groups with respect to pain and temperature control.

6. SAFETY

The Applicant carried out 3 studies to evaluate safety of the US formulation of Children's Advil Suspension.

6.1 Children's Analgesic Medicine Project (CAMP)

It was a multicentre, open study comparing Children's Advil (CA) with paracetamol suspension-Children's Tylenol (CT).

About 40% of patients were under two years of age and about 22% were enrolled during a well-child check up. The main reason for giving a study drug to those children was to treat symptoms arising from an immunisation (Table 9).

Table 9: Age Distribution of Patients in the Study

	SICK				WELL			
Age (yrs)	CA[a]	CT[a]	Both[a]	Total[b]	CA[a]	CT[a]	Both[a]	Total[b]
<1	33.3	64.2	2.5	520 (3.6%)	9.1	90.3	0.6	1859 (44.3%)
1-<2	64.2	32.5	3.3	3725 (25.4%)	23.7	75.1	1.2	1362 (32.4%)
2-<3	70.0	27.3	2.7	2422 (16.5%)	29.2	68.9	1.9	463 (11.0%)
3-<5	72.0	24.6	3.4	3142 (21.4%)	44.0	53.6	2.4	209 (5.0%)
5-<7	74.7	21.7	3.6	2107 (14.4%)	54.5	44.8	0.7	279 (6.7%)
7-<11	81.7	15.6	2.7	2140 (14.6%)	33.3	61.1	5.6	18 (0.4%)
11+	85.2	13.2	1.6	600 (4.1%)	37.5	62.5	0.0	8 (0.2%)
Total[c]	10352	3850	454	14656 (100%)	881	3274	43	4198 (100%)

	SICK	WELL
	70.6 % 26.3 % 3.1%	21.0 % 78.0 % 1.0%
	Number missing (sick): 59	Number missing (well): 8

a Numbers in the body of this column are row percents
b Numbers in this column are row totals and column percents
c Numbers in these two rows are column totals and row percents

The reason for use is summarised in Table 10.

Table 10: Reason for Use of Either CA or CT

Reason for Use	Number of Children
Otitis media, other ear infections	6090
Pharyngitis, tonsillitis, other sore throats	5787
Viral illness (roseola, chicken pox, etc.)	2403
Pain (headache, fracture, muscle pain, etc.)	2041
Other	1975
Upper respiratory symptoms or illness	1716
Bronchitis	1344
Pain prophylaxis associated with immunisation	1220
Sinusitis	736
Flu	375
Croup	271
Gastro-enteritis (stomach flu, etc.)	251
Pain (inflammatory)	238
Conjunctivitis	208
Asthma	108
Pneumonia	84
TOTAL	**24847**

Adverse drug events (ADE) experienced on either CA or CT groups were followed up in detail.

There were no severe adverse events. The most common adverse events were nausea/vomiting, rash, insomnia, abdominal pain, restlessness, diarrhoea and nervousness.

6.3 Study W-xyz

It was an open, multiple dose study to evaluate the safety of Children's Advil Ibuprofen Suspension when administered to children aged 2 to 12 years with various painful conditions (sore throat, earache, headache).

Children's Advil was administered at 10mg/kg every 6 hours, as needed, for up to 10 days. Fifty AEs were reported by 23% of patients (Table 11).

Table 11. Adverse Events

GI	(N)	Respiratory	(N)	Nervous	(N)	Body/Whole	(N)	Special Senses	(N)	Skin & appendages	(N)
Diarrhoea	2	Cough		Dizziness	1	Asthenia	2	Lacrimation disorder	1	Rash	4
Dyspepsia	2	Increase	2	Hyperkinesia	2	Chills	1				
Nausea	2	Pharyngitis	7	Paraesthesia	1	Fever	3	Pain, Ear	2		
Abd Pain	5	Rhinitis	2	Somnolence	7	Headache	3	Tinnitus	2		
Vomiting	7										

The study concluded that Children's Advil Suspension administered at 10mg/kg up to 4 times a day was safe for the relief of pain in children.

6.4 Boston Fever Study (Lesko and Mitchell, 1995)

It was a randomised, double blind study to assess the risk of rare serious adverse events (AEs) following the use of ibuprofen suspension in febrile children aged 6 months to 12 years.

The study evaluated 83 915 children who were randomised to receive either ibuprofen 5mg/kg (n=27 948), or ibuprofen 10mg/kg (n=27 837), or paracetamol 12mg/kg (n=28 130). The treatment was given every 4-6 hours up to five doses per day.

Median number of doses was between 6 and 10, with a median duration of 3 days treatment. The most common reasons for treatment were upper respiratory tract infections, otitis media, and pharyngitis.

The study focused on hospitalisation for acute gastrointestinal bleeding, acute renal failure, anaphylaxis, and the occurrence of Reye Syndrome. There was no significant difference between ibuprofen and paracetamol groups in the observed risk of gastrointestinal bleeding, acute renal failure and anaphylaxis. No cases of Reye Syndrome were seen. There was one death in the ibuprofen group due to bacterial meningitis.

6.5 Periodic Safety Update Report

The Periodic Safety Update Report for Children's Advil Suspension 100mg/5ml has been submitted.

The analysis of the Periodic Safety Update Report concluded that no new adverse events were reported and no amendments were required to the SPC for Children's Advil Suspension.

6.6 Safety of Ibuprofen in the Studies Submitted with this Application

Analysis of the Adverse Events (AEs) in the studies submitted indicates that the majority of adverse events are included in the labelling.

6.7 Other Safety Data

The Applicant reviewed published studies on gastrointestinal safety, renal adverse reactions and interactions, elderly and pregnancy.

The AEs reported in the published literature submitted with this application have been included in the proposed SPC/PIL.

7. EXPERT REPORT

The Clinical Expert Report was prepared by a suitably qualified person. It was concluded that a comparison of the benefits versus the risk of using Children's Advil Sugar Free Suspension to provide relief from the indications as detailed for self-medication in children aged six months and older is positive.

8. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC is provided and is satisfactory.

9. PATIENT INFORMATION LEAFLET (PIL)

The PIL is provided and is satisfactory. The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

10. LABELLING

The labelling is provided and is satisfactory.

11. MARKETING AUTHORISATION APPLICATION (MAA)

The MAA form is provided and is satisfactory.

12. DISCUSSION

This is an abridged application for ibuprofen suspension in children from the age of 6 months and is made according to Article 10 of Directive 2001/83/EC as amended.

The clinical section contains original data investigating pharmacokinetics, efficacy and safety of Children's Advil Sugar Free Suspension.

The efficacy and safety data submitted indicate that Children's Advil Sugar Free Suspension is safe and effective in the treatment of mild to moderate pain and fever in children aged 6 months and over.

13. CONCLUSIONS

The efficacy and safety of the product are considered satisfactory for the grant of a Marketing Authorisation.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Advil Ibuprofen Sugar Free 100mg/5ml Oral Suspension are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Advil Ibuprofen Sugar Free 100mg/5ml Oral Suspension and Nurofen Tablets 200mg (Crookes Healthcare Ltd).

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with ibuprofen is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

ADVIL IBUPROFEN SUGAR FREE 100MG/5ML ORAL SUSPENSION

PL 00165/0366

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 23rd November 2005.
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 14th December 2005.
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 13th November 2006, 22nd November 2007 and 4th January 2008 and further information relating to the quality dossiers on 9th February 2006, 21st October 2006 and 12th December 2006.
4	The applicant responded to the MHRA's requests, providing further information on 6th November 2007, 7th December 2007 and 8th January 2008 for the clinical sections, and again on 21st October 2006 and 20th June 2007 for the quality sections.
5	The applications were determined on 27th February 2008.

ADVIL IBUPROFEN SUGAR FREE 100MG/5ML ORAL SUSPENSION

PL 00165/0366

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5mL contains 100mg Ibuprofen.

Excipients

Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension contains 2000mg (2g)

maltitol liquid per 5mL.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Suspension.

Opaque, whitish suspension with an odour of banana.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the relief of mild to moderate pain including rheumatic or muscular pain, sore throat, earache, headache, toothache, teething pain, feverishness and symptoms of colds and influenza.
For the reduction of post immunisation pyrexia.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

For oral administration and short-term use only.
The minimum effective dose should be used for the shortest time necessary to relieve symptoms.
For children weighing 7kg or more: 20mg/kg body weight daily in divided doses.
Shake the bottle vigorously before measuring the dose. To open the cap, press firmly on the tag and lift as indicated. Completely insert the syringe and draw up the required amount of liquid by reading the volume markings on the syringe.
Administer the dose by introducing the tip of the syringe into the mouth of the infant/child, then apply a light pressure on the plunger to release the suspension gradually.
Wash the syringe after use with warm water and let it dry, keeping it out of reach of children.
Infants 6 months to 1 year: 2.5ml 3 times in 24 hours.
Infants 1 to 2 years: 2.5ml 3-4 times in 24 hours.
Children 3 to 7 years: 5ml 3-4 times in 24 hours.
Children 8 to 12 years: 10ml 3-4 times in 24 hours.
For post immunisation pyrexia: one 2.5ml dose followed by one further 2.5ml dose 6 hours later if necessary. If the fever is not reduced, consult your doctor.

Not to be given to children under 6 months of age.
If the child's symptoms persist for more than 3 days, consult a doctor.
Leave at least four hours between doses and do not exceed the recommended dose.

4.3 CONTRAINDICATIONS

Hypersensitivitye to ibuprofen or to any of the constituents in the product.
Ibuprofen is contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis or urticaria) in response to aspirin or other nonsteroidal anti-inflammatory drugs.
Active or previous peptic ulcer.
History of upper gastrointestinal bleeding or perforation, related to previous NSAID therapy.

Patients with severe hepatic failure, severe renal failure or severe heart failure. (See section 4.4)
Use with concomitant NSAIDs including cyclo-oxygenase-2 specific inhibitors (See section 4.5).
Use in third trimester of pregnancy.
Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Caution is required in patients with certain conditions:
- systemic lupus erythematosus as well as those with mixed connective tissue disease due to increased risk of aseptic meningitis (see section 4.8).
- gastrointestinal disorders and chronic inflammatory intestinal disease as these conditions may be exacerbated (ulcerative colitis, Crohn's disease) (see section 4.8).
- oedema, hypertension and/or cardiac impairment as renal function may deteriorate and/or fluid retention occur (see section 4.5).
- renal impairment as renal function may deteriorate (see sections 4.3 and 4.8).
- hepatic dysfunction (see sections 4.3 and 4.8).

Bronchospasms may be precipitated in patients suffering from or with a previous history of bronchial asthma or allergic disease.
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see GI and cardiovascular risks below).
The elderly are at increased risk of the serious consequence of adverse reactions.
GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.
When GI bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn immediately.
Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the intial stages of treatment.
Caution should be advised in patients receiving concomitant medications, which could increase the risk of gastrotoxicity or bleeding, such as corticosteroids, or anticoagulants such as warfarin or anti-platelet agents such as aspirin (see section 4.5).
There is limited evidence that drugs, which inhibit cyclo-oxygenase/ prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible upon withdrawal of treatment.

Cardiovascular and cerebrovascular effects:

Clinical trial and epidemiological data suggest that use of ibuprofen, particularly at high doses (2,400 mg 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. ≤ 1,200 mg daily) is associated with an increased risk of myocardial infarction.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Ibuprofen should not be used in combination with:

Aspirin: unless low dose aspirin (not above 75 mg daily) has been advised by a doctor, as this may increase the risk of adverse reactions (see section 4.3).
Other NSAIDs: as these may increase the risk of adverse effects (see section 4.3).

Ibuprofen should be used with caution in combination with:

Anticoagulants: NSAIDs may enhance the effect of anticoagulants, such as warfarin (see section 4.4).
Antihypertensives and diuretics: NSAIDs may diminish the effects of these drugs.

Corticosteroids: may increase the risk of adverse reactions, especially of the gastrointestinal tract (see section 4.4).
Lithium: there is evidence for potential increases in plasma levels of lithium.
Methotrexate: there is a potential for increased plasma levels of methotrexate.
Zidovudine: there is evidence of an increased risk of haemarthroses and haematoma in HIV-positive haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

4.6 PREGNANCY AND LACTATION

While no teratogenic effect has been demonstrated in animal experiments, the use of Ibuprofen should, if possible, be avoided during the first 6 months of pregnancy. During the third trimester ibuprofen is contraindicated as there is a risk of premature closure of the foetal ductus arteriosus with possible persistent pulmonary hypertension. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child. (See section 4.3).
In limited studies ibuprofen appears in breast milk in very low concentrations and is unlikely to affect the breast-fed infant adversely.
See section 4.4 regarding female fertility.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

None expected at recommended doses and duration of therapy.

4.8 UNDESIRABLE EFFECTS

Hypersensitivity reactions have been reported and these may consist of:
(a) Non-specific allergic reactions and anaphylaxis
(b) Respiratory tract reactivity, eg asthma, aggravated asthma, bronchospasm, dyspnoea
(c) Various skin reactions, e.g. pruritus, urticaria, angioedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis, erythema multiforme)
The following list of adverse effects relates to those experienced with ibuprofen at OTC doses, for short-term use. In the treatment of chronic conditions, under longterm treatment, additional adverse effects may occur.

Infections and Infestations	Very rare	Aseptic meningitis
Blood and lymphatic disorders	Very rare	Haematopoietic disorders (anaemia, hemolytic anemia, aplastic anemia), leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, nose and skin bleeding.
Immune system Disorders	Uncommon	Hypersensitivity reactions with urticaria and pruritus.
	Very rare	In patients with existing auto-immune (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. Severe hypersensitivity reactions. Symptoms

		could be: facial, tongue and larynx swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock). Exacerbation of asthma and bronchospasm.
Psychiatric Disorders	Very rare	Nervousness
Nervous System	Uncommon	Headache
Eye disorders	Very rare	Visual disturbance
Ear and labyrinth Disorders	Very rare	Tinnitus and vertigo
Cardiac disorders	Very rare	Cardiac failure
Vascular disorders	Very rare	Hypertension
Respiratory, Thoracic and mediastinal Disorders	Very rare	Asthma, broncospasm, dyspnoea And wheezing
Gastrointestinal Disorders	Uncommon	Abdominal pain, dyspepsia and nausea.
	Rare	Diarrhoea, flatulence,constipation andvomiting
	Very rare	Peptic ulcer, perforation or gastrointestinal haemorrhage,sometimes fatal, particularly in the elderly (see section 4.4). Exacerbation of ulcerative colitis and Crohn's disease (see section 4.3). Mouth ulceration.
Hepatobiliary Disorders	Very rare	Liver disorders, especially in long-term treatment, hepatitis and jaundice
Skin and subcutaneous tissue disorders	Uncommon	Various skin rashes
	Very rare	Severe forms of skin reactions such as erythema multiforme and epidermal necrolysis can occur.
Renal and urinary Disorders	Very rare	Acute renal failure, papillary

		necrosis, especially in long-term use, associated with increased serum urea and oedema.
General disorders and administration site conditions	Very rare	Oedema, peripheral oedema
Investigations	Very rare	Decreased hematocrit and hemoglobin levels

Oedema, hypertension, and cardiac failure have been reported in association with NSAID treatment.
Clinical trial and epidemiological data suggest that use of ibuprofen (particularly at high doses 2,400 mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

4.9 OVERDOSE

In children ingestion of more than 400 mg/kg may cause symptoms. In adults the dose response effect is less clear-cut. The half-life in overdose is 1.5-3 hours.

Symptoms

Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as vertigo, headache, respiratory depression, dyspnoea, drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning, hypotension, hyperkalaemia, and 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.

Management

Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC code: M01A E01

Ibuprofen is a propionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. In humans ibuprofen reduces inflammatory pain, swellings and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

5.2 PHARMACOKINETIC PROPERTIES

Ibuprofen pharmacokinetics have been well studied over the proposed dosage range in both children and adults and these data are frequently referenced in general textbooks and specialty publications. Overall, the drug's pharmacokinetic profile in children is similar to that in adults.

Ibuprofen is rapidly absorbed following administration and is rapidly distributed throughout the whole body. The excretion is rapid and complete via the kidneys.

Maximum plasma concentrations are reached 45 minutes after ingestion if taken on an empty stomach. When taken with food, peak levels are observed after 1 to 2 hours.

These times may vary with different dosage forms.

The half-life of ibuprofen is approximately 2 hours.
In limited studies, Ibuprofen appears in the breast milk in very low concentrations.

5.3 PRECLINICAL SAFETY DATA
No relevant information additional to that already contained elsewhere in the SPC.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Glycerol
Xanthan Gum
Maltitol Liquid
Polysorbate 80
Sodium Benzoate (E211)
Disodium Edetate
Citric Acid Anhydrous
Saccharin Sodium
Acesulfame Potassium
Purified Water
Strawberry Flavour 11407-33
Banana Flavour 10995-36.

6.2 INCOMPATIBILITIES
None known.

6.3 SHELF LIFE
2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
No special precautions for storage.

6.5 NATURE AND CONTENTS OF CONTAINER
100 ml glass bottles with a child-resistant polypropylene closure or a polypropylene cap with a natural low-density polyethylene liner.
Oral syringe (polyethylene body and white printed polystyrene piston), marked for 2.5 and 5 ml dose.
Crystal polystyrene measuring spoon, 5ml capacity with a moulded 2.5ml mark
Polypropylene dosing spoon with double bowls of 2.5ml and 5ml capacity.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special precautions.

7 MARKETING AUTHORISATION HOLDER
Whitehall Laboratories, Huntercombe Lane South, Taplow, Berkshire SL6 0PH, UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 0165/0366

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
27/02/2008

10 DATE OF REVISION OF THE TEXT
27/02/2008

PATIENT INFORMATION LEAFLET

Advil®

Ibuprofen Sugar Free 100mg / 5mL Oral Suspension
Contains Ibuprofen

Read all of this leaflet carefully because it contains important information for you.
This medicine is available without prescription. However, you still need to use it carefully to get the best results from it.
- Keep this leaflet. You might need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must contact a doctor if your child's symptoms worsen or do not improve after 3 days.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT ADVIL IBUPROFEN SUGAR FREE 100MG/5ML ORAL SUSPENSION IS AND WHAT IT IS USED FOR

Each 5mL of Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension contains 100mg of ibuprofen. Ibuprofen belongs to a group of medicines called Non Steroidal Anti-inflammatory Drugs (known as NSAID's), that work by relieving pain, and reducing inflammation, swelling and fever. Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension provides fast, effective relief from mild to moderate pain including rheumatic or muscular pain, sore throat, earache, headache, toothache, teething pain, and symptoms of colds and flu. It is also indicated for the reduction of fever including that following immunisation.

2. BEFORE YOU USE ADVIL IBUPROFEN SUGAR FREE 100MG/5ML ORAL SUSPENSION

Please read the following information.
Do not give Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension to babies or children who:
- have or have ever had a stomach ulcer or perforation, or bleeding from the stomach
- have severe heart, kidney or liver disease
- are allergic to ibuprofen or any other ingredient of the product (see Section 6), aspirin or other related painkillers
- are taking other NSAID painkillers, or aspirin with a daily dose above 75mg

Talk to your doctor or pharmacist before giving Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension to your child if he/she is:
- taking anticoagulants, or any water tablets, tablets for blood pressure, corticosteroids, or lithium, methotrexate or zidovudine
- asthmatic, or suffers from kidney, heart or liver problems, or any allergic reactions which cause skin rashes, joint pain or fever

The above also applies to adults who wish to take Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension.
Medicines such as Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke. Any risk is more likely with high doses and prolonged treatment. Do not exceed the recommended dose or duration of treatment (not more than 3 days without consulting a doctor).
If your child has heart problems or previous stroke, or you think that he/she might be at risk of these conditions (for example if they have high blood pressure, diabetes or high cholesterol), you should discuss their treatment with your doctor or pharmacist.

Pregnancy and breast-feeding
Do not take Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension if you are in the last 3 months of pregnancy.
Talk to your doctor or pharmacist before taking Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension if you are:
- trying to become pregnant (ibuprofen belongs to a group of medicines, NSAIDs, which may impair fertility in women. This effect is reversible upon stopping the medicine)
- in the first 6 months of pregnancy, or if you are breast-feeding.

Important information about one of the ingredients of Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension:
Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension contains maltitol liquid. If you have been told by your doctor that your child has an intolerance to some sugars, contact your doctor before giving him/her this medicinal product.

3. HOW TO USE ADVIL IBUPROFEN SUGAR FREE 100MG/5ML ORAL SUSPENSION

The minimum effective dose should be used for the shortest time necessary to relieve symptoms. Shake the bottle vigorously before measuring the dose. An oral dosing syringe marked for 2.5ml and 5ml doses is provided to ensure dosing accuracy.

/please turn over

To open the cap, press firmly on the tag and lift as indicated. Completely insert the syringe and draw up the required amount of liquid by reading the volume markings on the syringe. Administer the dose by introducing the tip of the syringe into the mouth of the infant/child, then apply a light pressure on the plunger to release the suspension gradually.
Wash the syringe after use with warm water and let it dry, keeping it out of reach of children.

Age	Dose
6 months - 12 months:	2.5ml 3 times in 24 hours
1 year - 2 years:	2.5ml 3-4 times in 24 hours
3 years - 7 years:	5ml 3-4 times in 24 hours
8 years - 12 years:	10ml 3-4 times in 24 hours

Post-immunisation Fever: One 2.5ml dose followed by one further 2.5ml dose 6 hours later if necessary. If the fever is not reduced, consult your doctor.
Do not give to infants under 6 months of age.
Leave at least 4 hours between doses and do not exceed the recommended dose.
If your child's symptoms persist for more than 3 days consult your doctor.
If you use or take more Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension than you should:
Contact your doctor or hospital immediately.
Bring the remaining medicine (or empty bottle) with you to show the doctor.

4. POSSIBLE SIDE EFFECTS:

Like all medicines, Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension can cause side effects, although not everybody gets them. If you notice any of the following side effects stop using this medicine immediately.

Less than 1 in 100 children may experience the following uncommon side-effects:
- **Allergic Reactions:** Hives, skin rashes and itching.
- **Stomach:** Abdominal pain, indigestion, heartburn and nausea.
- **Nervous system:** Headache.

Less than 1 in 1000 children may experience the following rare side effects:
- Diarrhoea, wind, constipation and vomiting
- Hearing disturbances

Less than 1 in 10,000 children may experience the following very rare side effects:
- Reduction in blood cells, which can make the skin pale or yellow, cause fever, sore throat, mild mouth ulcers, flu-like symptoms, exhaustion or weakness, easy bruising, or bleeding from the skin or nose.
- Inflammation of the brain lining. Symptoms could include stiff neck, headache, nausea, vomiting, fever or feeling disorientated.
- Severe allergic reactions. Symptoms could include dizziness or fainting, faster heart rate, swelling of the face, tongue and throat.
- High blood pressure.
- Worsening of asthma and wheezing or difficulty in breathing.
- Nervousness, visual disturbance, ringing in the ears and vertigo.
- Peptic ulceration or perforation. Symptoms could include severe abdominal pain, vomiting blood (or liquid with what looks like coffee grounds), blood in the faeces (stools/motions) or passing black tarry stools.
- Liver problems. Symptoms could include yellowing of the skin or the whites of the eyes.
- Kidney problems. Symptoms could include swelling of the ankles.
- Severe skin reactions. Symptoms could include blistering.

Medicines such as Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke.
Please note that using the smallest dose required can reduce the chances of experiencing side effects. Side effects may be more serious in elderly patients.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE ADVIL IBUPROFEN SUGAR FREE 100MG/5ML ORAL SUSPENSION

- Do not use Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension after the expiry date, which is stated on the bottom of the carton.
- Keep out of reach and sight of children.

6. FURTHER INFORMATION

What does this medicine contain?
The active substance is ibuprofen. Each 5mL of Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension contains 100mg of ibuprofen.
In addition, Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension contains Glycerol, Xanthan Gum, Maltitol Liquid, Polysorbate 80, Sodium Benzoate (E211), Disodium Edetate, Citric Acid, Sodium Saccharin, Acesulfame Potassium, Purified water, Strawberry and Banana Flavour.
Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension is available in bottles containing 100mL of liquid suspension. The suspension is opaque with a whitish colour and an odour of banana.

Who makes this medicine?
Marketing Authorisation Holder: Whitehall Laboratories, Huntercombe Lane South, Taplow, Berkshire SL6 0PH, UK
Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension is manufactured by: Wyeth Pharmaceuticals, New Lane, Havant, Hampshire, PO9 2NG, UK.

This leaflet was last approved in (MM/YYYY)

* Trade Mark

XP12020A09

LABELLING

1. NAME OF THE MEDICINAL PRODUCT

Advil Ibuprofen Sugar Free 100 mg/ 5 ml Oral Suspension

2. STATEMENT OF ACTIVE SUBSTANCE(S)

100 mg Ibuprofen per 5 ml

3. PHARMACEUTICAL FORM AND CONTENTS

Oral Suspension
100 ml

4. LIST OF EXCIPIENTS

Glycerol, Maltitol Liquid, Sodium Benzoate E211, Sodium Saccharin,

5. METHOD AND ROUTE (S) OF ADMINISTRATION

For oral administration only. With dosing syringe.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep all medicines out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read the enclosed leaflet before giving this product to your child.
Do not exceed the stated dose:
For short term use only

As with all medicines, talk to your doctor or pharmacist if your child is receiving medical treatment or is taking any other medicines.

Do not give it to your child if he/she

- has or has ever had a stomach ulcer or perforation, or bleeding from the stomach
- is allergic to ibuprofen or any other ingredient of the product, aspirin or other related painkillers
- is taking other NSAID painkillers, or aspirin with a daily dose above 75mg.

Speak to a pharmacist or your doctor before giving this product to your child if he/she

- has asthma, liver, heart, kidney or bowel problems

If your child's symptoms worsen or persist for more than 3 days, consult your doctor.

This product contains maltitol liquid. If you have been told by your doctor that your child has an intolerance to some sugars, contact your doctor before giving this medicinal product.

Adults considering taking this product should also consider these factors, and pregnant women should obtain medical advice before use.

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

No special precautions for storage

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

None

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Whitehall Laboratories Ltd, Huntercombe Lane South, Taplow, Berkshire SL6 0PH

12. MARKETING AUTHORISATION NUMBER(S)

PL 0165/0366

13. MANUFACTURER'S BATCH NUMBER

<Lot> {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product not subject to medical prescription

15. INSTRUCTIONS ON USE

Directions: READ THE LEAFLET CAREFULLY BEFORE USE.
Shake the bottle vigorously before measuring the dose. An oral dosing syringe marked for 2.5ml and 5ml dose is provided to ensure dosing accuracy.

To open the cap, press firmly on the tag and lift as indicated. Completely insert the syringe and draw up the required amount of liquid by reading the volume markings on the syringe.

Administer the dose by introducing the tip of the syringe into the mouth of the infant/child, then apply a light pressure on the plunger to release the suspension gradually.

Wash the syringe after use with warm water and let it dry, keeping it out of reach of children.

Age	**Dose**
6 months - 12 months:	2.5ml 3 times in 24 hours
1 year - 2 years:	2.5ml 3-4 times in 24 hours
3 years - 7 years:	5ml 3-4 times in 24 hours
8 years - 12 years:	10 ml 3-4 times in 24 hours

Post-immunisation Fever: one 2.5ml dose followed by one further 2.5ml dose 6 hours later if necessary. If the fever is not reduced, consult your doctor.

OTHER INFORMATION TO APPEAR ON THE PACK

Relieves fever and pain in babies & children
From 6+ months
Accurate and Easy Dosing
Strawberry & banana flavour
Sugar and colour free

Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension is specially formulated for the fast and effective relief of fever and pain in children and babies over 6 months. Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension has a strawberry and banana flavour and provides reduction in temperature and relief from fever.

The dosing system ensures that you give your child the correct amount of Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension to soothe away the pain from sore throat, earache, headache, teething pain, toothache and rheumatic or muscular pain. Advil Ibuprofen Sugar Free 100mg/5mL Oral Suspension also reduces fever associated with immunisation and symptoms of colds and flu.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Advil Ibuprofen Sugar Free 100 mg/ 5 ml Oral Suspension

Ibuprofen

2. STATEMENT OF ACTIVE SUBSTANCE(S)

100 mg Ibuprofen per 5 ml

3. PHARMACEUTICAL FORM AND CONTENTS

Oral Suspension
100 ml

4. LIST OF EXCIPIENTS

Glycerol, Maltitol Liquid, Sodium Benzoate E211, Sodium Saccharin.

5. METHOD AND ROUTE (S) OF ADMINISTRATION

For oral administration only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep all medicines out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read the enclosed leaflet before giving this product to your child.

Do not exceed the stated dose:
For short term use only

As with all medicines, talk to your doctor or pharmacist if your child is receiving medical treatment or is taking any other medicines.

Do not give it to your child if he/she

- has or has ever had a stomach ulcer or perforation, or bleeding from the stomach
- is allergic to ibuprofen or any other ingredient of the product, aspirin or other related painkillers
- is taking other NSAID painkillers, or aspirin with a daily dose above 75mg.

Speak to a pharmacist or your doctor before giving this product to your child if he/she

- has asthma, liver, heart, kidney or bowel problems

If your child's symptoms worsen or persist for more than 3 days, consult your doctor.

This product contains maltitol liquid. If you have been told by your doctor that your child has an intolerance to some sugars, contact your doctor before using this medicine.

Adults considering taking this product should also consider these factors, and pregnant women should obtain medical advice before use.

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

No special precautions for storage

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

None

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Whitehall Laboratories Ltd, Huntercombe Lane South, Taplow, Berkshire SL6 0PH

12. MARKETING AUTHORISATION NUMBER(S)

PL 0165/0366

13. MANUFACTURER'S BATCH NUMBER

<Lot> {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product not subject to medical prescription

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