

**PARAMED IBUPROFEN FOR CHILDREN 100 MG/5 ML
ORAL SUSPENSION & ORAL SUSPENSION SACHETS**

PL 12063/0060-1

UKPAR

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**PARAMED IBUPROFEN FOR CHILDREN 100 MG/5 ML
ORAL SUSPENSION & ORAL SUSPENSION SACHETS**

PL 12063/0060-1

LAY SUMMARY

The MHRA granted Wrafton Laboratories Limited Marketing Authorisations (licences) for the medicinal products Paramed Ibuprofen For Children 100mg/5ml Oral Suspension and Oral Suspension Sachets (PL 12063/0060-1) on 7th September 2006. These products are to be sold as a Pharmacy only medicine (PL 12063/0060) which is presented in a bottle and a General Sales List product (PL 12063/0061) which is presented in a sachet.

Paramed Ibuprofen For Children 100mg/5ml Oral Suspension contain the active ingredient Ibuprofen.

This application is claiming essential similarity to Junifen suspension 100mg/5ml (PL 00327/0077). The licence was granted on the 11th August 1993 and was held by Crookes Healthcare Limited. Junifen suspension 100mg/5ml has been replaced on the market by Nurofen For Children 100mg/5ml oral suspension (PL 00327/0085) and as such these products can be used interchangeably.

No new or unexpected safety concerns arose from this abridged application and it was, therefore, judged that the benefits of taking Paramed Ibuprofen For Children 100mg/5ml Oral Suspension and Oral Suspension Sachets outweighs the risk, hence a Marketing Authorisation has been granted.

**PARAMED IBUPROFEN FOR CHILDREN 100 MG/5 ML
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SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted a marketing authorisation for the medicinal products Paramed Ibuprofen for Children 100mg/5ml Oral Suspension and Oral Suspension Sachets (PL 12063/0060-1) to Wrafton Laboratories Limited on 7th September 2006. The Pharmacy only medicine (PL 12063/0060) is presented in a bottle and the General Sales List product (PL 12063/0061) is presented in a sachet.

These applications were submitted as abridged applications according to article 10.1 [formerly Article 10.1(a)(iii)] of Directive 2001/83/EC, cross-referring to Junifen suspension 100mg/5ml (PL 00327/0077). The licence was granted on the 11th August 1993 and was held by Crookes Healthcare Limited. Junifen suspension 100mg/5ml has been replaced on the market by Nurofen For Children 100mg/5ml oral suspension (PL 00327/0085).

This product contains the active ingredient Ibuprofen which is used for the fast and effective reduction of fever, including post immunisation pyrexia, cold and flu symptoms, and the fast and effective relief of mild to moderate pain, such as sore throat, teething pain, toothache, earache, headache, minor aches and sprains.

PHARMACEUTICAL ASSESSMENT

Our Reference:	PL 12063/0060 - 0001
Product:	PL 12063/0060 WRAFTON LABS IBUPROFEN ORAL SUSPENSION 100MG/5ML
Marketing Authorisation Holder:	WRAFTON LABORATORIES LIMITED
Active Ingredient(s):	IBUPROFEN.
Type of Procedure:	National
Submission Type:	Initial
Submission Category:	Abridged
Submission Complexity:	Standard

1. INTRODUCTION

These are abridged applications for Marketing Authorisations in the UK submitted under Article 10.1 [formerly Article 10.1(a)(iii)] of Directive 2001/83/EC, for products claiming essential similarity to Junifen suspension 100mg/5ml (PL 00327/0077). The licence was granted on the 11th August 1993 and was held by Crookes Healthcare Limited. Junifen suspension 100mg/5ml has been replaced on the market by Nurofen For Children 100mg/5ml oral suspension (PL 00327/0085). The Nurofen For Children 100mg/5ml oral suspension licence is a standard abridged application of the cross referenced Junifen suspension 100mg/5ml. Nurofen For Children 100mg/5ml suspension was used as the medicinal product in the bioequivalence study.

The Pharmacy only medicine (PL 12063/0060) is presented in a bottle and the General Sales List product (PL 12063/0061) is presented in a sachet.

2. DRUG SUBSTANCE

2.1 General information

Details of the drug substance supplier have been supplied. A Certificate of Suitability granted 12th February 2001, has been supplied, with permission for use with Ibuprofen products from the manufacturer.

The re-test date on the certificate of suitability is three years if stored in lock-rim fibre drums. Certificates of analysis have been provided for batches tested at the manufacturer of the drug substance.

2.2 Manufacture

2.2.1 Manufacturers

Details of the drug substance manufacturer have been supplied.

2.3 Control of drug substance

2.3.1 Specification

The specifications provided for ibuprofen are supplied. These include the requirements of the European Pharmacopoeia. The specifications are taken from the manufacturer's certificate of analysis, which includes the additional requirements of the certificate of suitability.

2.3.2 Container closure system

The material is packed in lock-rim fibre drums.

3. DRUG PRODUCT

3.1 Composition

The composition of the suspension is summarised in table 2. The suspension is an opaque white to off-white, orange flavoured viscous suspension. The suspension is packed in a polyethylene terephthalate (PET) amber coloured bottle containing 100ml or 150ml with a high density polyethylene child-resistant cap fitted with a polypropylene inner layer and insert comprising folding boxboard/paper/aluminium foil/wax disc or laminate sachets consisting of Surlyn Ionomer/low density polyethylene/aluminium paper.

Table 2

Name of Ingredients	Reference
Active	
Ibuprofen	Ph Eur
Excipients	
Polysorbate 80	Ph Eur
Maltitol liquid	Ph Eur
Acesulfame potassium	Ph Eur
Sodium cyclamate	Ph Eur
Xanthan gum	Ph Eur
Glycerol	Ph Eur
Sodium benzoate	Ph Eur
Disodium edetate	Ph Eur
Anhydrous citric acid	Ph Eur
Orange flavour F/32297	In-house spec
Purified water	Ph Eur

3.2 Pharmaceutical Development

The compatibility of ibuprofen in combination with the excipients has been demonstrated by cross referral to the finished product stability data, highlighting the fact that there was no evidence of physical or chemical deterioration within the study. The stability data was also used to show that the ibuprofen at the selected particle size stays in suspension and produces a consistent product.

The excipients used are frequently used in these types of preparations and are at standard concentrations. The function of each excipient has been stated with reasons for selection in preference to suitable alternatives.

There are no overages in the formulation.

3.3 Manufacture

3.3.1 Manufacturer(s)

The manufacturer has been stated.

For the sachets there is also the possibility that sachet filling and sealing can occur at another site and details of this have been provided.

3.3.2 Batch formula

The batch formulas have been provided. The proposed maximum batch size for production and the typical batch size have been stated. There is no overage of ingredients used.

3.3.3 Manufacturing process and process controls

A flow diagram detailing the manufacturing process has been provided. A written summary of the process has also been included for the different batch sizes.

3.3.4 In-process controls

Appropriate in-process controls have been described.

3.3.5 Control of critical steps and intermediates

Appropriate details of critical steps and intermediates have been provided.

3.3.6 Process validation or evaluation

The data presented demonstrates that adequate controls are in place to manufacture the ibuprofen suspension and fill it into both bottles and sachets in a reproducible fashion at the pilot scale. The processes used are standard processes for the manufacturer. Consequently, the validation data provided is sufficient.

3.4 Control of excipients

3.4.1 Specification

Most of the excipients have monographs in the European Pharmacopoeia. A certificate of analysis from each of the respective raw material manufacturers has been supplied. The analytical procedures are stated as those detailed in the Pharmacopoeia with adequate validation being performed. The finished product manufacturer performs limited testing when supplied with a certificate of analysis or full testing when not supplied with a certificate of analysis. The methods used are pharmacopoeia methods and as such no validation data has been supplied.

MHRA PAR Paramed Ibuprofen for Children 100 mg/5 ml Oral Suspension & Oral Suspension Sachets PL 12063/0060-1

3.4.2 Novel excipients

The orange flavour F/32297 is a food grade product compliant with Directive 83/388/EEC. A partial breakdown of the ingredients is supplied with the in-house specifications and a certificate of analysis from the supplier. A declaration of conformity with Directive 83/833/EEC and a TSE declaration have also been supplied.

3.5 Control of drug product

3.5.1 Specification

Finished product specifications for this product have been provided

Ibuprofen suspension has a British Pharmacopoeia specification. The proposed finished product specification fulfils the requirements of the pharmacopoeia specification with an alternative test being used for identification.

The microbiology testing is performed on every batch at release.

3.5.2 Analytical procedures

In-house methods have been supplied for appearance, odour, viscosity, specific gravity and weight, pH, identification, taste, assay of sodium benzoate, assay of ibuprofen, assay of 4-isobutylacetophenone and dissolution.

The dissolution method is based on the method in the USP.

3.5.3 Validation

The HPLC method for assay of ibuprofen and sodium benzoate has been validated. The method has precision and accuracy.

The only validation performed in relation to the dissolution method is that relating to the HPLC analysis of samples.

Acceptable validation data in relation to the microbiology methods used to assess the quality of the suspension have been provided demonstrating recovery of specified organisms in the presence of the product.

3.5.4 Batch analyses

Batch analyses of the batches manufactured during validation of the process are provided. These batches have also been placed on stability. There is reference to the batches of drug substance used in each batch of Ibuprofen paediatric suspension.

3.6 Container closure system

The packaging used for the 100ml or 150ml presentation comprises an amber coloured polyethylene terephthalate (PET) bottle with child-resistant caps. The caps are high density polyethylene outers which are lined inside with polypropylene. There is a disc shaped multi-layered liner inside the cap which is folding boxboard/paper/aluminium foil/wax with the aluminium foil/wax as the product contact layer.

The packaging used for the 5ml presentation comprises a laminate sachet of Surlyn ionomer (contact material)/low density polyethylene/8 micron aluminium/paper.

Both presentations are supplied with a CE marked double-ended spoon with measures of 2.5ml and 5ml.

The finished product manufacturer tests the bottle and cap for appearance when supplied accompanied with a suitable certificate of analysis or certificate of conformity.

The sachet is tested for appearance and IR identity when supplied accompanied with a suitable certificate of analysis or certificate of conformity.

The product was assessed for extractables after contact between the packaging and the product under extreme conditions. No extractables are shown to interfere with the analysis of ibuprofen, sodium benzoate or 4-isobutylacetophenone. The packaging materials are in compliance with the relevant guidelines on migration limits with relevant certification presented.

3.7 Stability

Bottles

Two batches have been put on to stability, with the batches utilising two batches of drug substance. The storage conditions are 25°C/60%RH (12 months) and 40°C/75%RH (6 months).

The batches were assessed on the basis of the shelf-life specification. Microbiological testing was performed initially and then at each 6 monthly interval.

The data provided demonstrates that the Ibuprofen paediatric suspension is stable in the 100ml PET bottles with respect to the physical, chemical and microbiological properties when stored at 25°C/60%RH for 24 months and 40°C/75%RH for 6 months. The stability study is set to continue at 25°C/60%RH up to 36 months. The influence of time and storage conditions on sedimentation has not been discussed.

The applicant is proposing a shelf life of 36 months without any special precautions for storage, with the intention of extending this time when more data becomes available. This is acceptable.

A commitment has been made that the full-scale production batches will go on to stability.

Sachets

Two batches have been put on to stability, with the batches utilising two batches of drug substance. The storage conditions are 25°C/60%RH (12 months), 30°C/60%RH (12 months) and 40°C/75%RH (6 months).

The batches were assessed on the basis of the shelf-life specification. Microbiological testing was performed initially and then at 6, 9 and 12 months.

The applicant is proposing a shelf life of 24 months with the special precaution for storage of 'Do not store above 25°C', with the intention of extending this time when more data becomes available. This is acceptable.

3.8 Other information

3.8.1 Bioanalytical methods

Validation of the method has been performed. It has been demonstrated that the method is selective for ibuprofen. The method has also been shown to be precise and accurate.

3.8.2 Bioequivalence

A bioequivalence study was performed. This was a comparative, randomised, single-dose, crossover study. Comparing the Ibuprofen 100mg/5ml suspension with Nurofen For Children 100mg/5ml suspension in healthy adults. Twenty one subjects were enrolled in the study. Data was analysed for twenty due to one withdrawal. The batch of Ibuprofen 100mg/5ml suspension is at least 10% of the proposed maximum batch size.

The confidence intervals derived are within the 80% to 125% acceptance range of the Notes for Guidance on Bioavailability and Bioequivalence. Ibuprofen 100mg/5ml suspension was therefore considered to be bioequivalent to Nurofen For Children 100mg/5ml suspension at a dose of 400mg ibuprofen.

3.8.3 Essential similarity

The dissolution profiles of the Ibuprofen 100mg/5ml suspension are comparable to Nurofen for Children 100mg/5ml suspension. This has been conducted only on the batches used in the bioequivalence study.

No discussion on the chemical essential similarity has been presented. It has been demonstrated that no degradation products are formed on stressed samples of the finished product. The product is analysed for the appropriate degradant as detailed in the pharmacopoeia monograph and shown to be compliant. The impurities from the active substance are controlled by the pharmacopoeia monograph. The control presented and the stability of the product justifies the omission of a comparison.

4. PRODUCT LITERATURE

4.1 SPC

The SPC is in compliance with the guidelines and quality section.

4.2 PIL

The PIL is in compliance with the SPC and guidelines.

4.3 LABEL

The labels are in compliance with the SPC and guidelines.

5. ADMINISTRATIVE

5.1 MAA form

The MAA form is in compliance with the SPC and guidelines.

5.2 Quality Overall Summary

The report is a summary of the module and is satisfactory.

6. CONCLUSIONS AND ADVICE

A marketing authorisation can be granted.

Pharmaceutical Assessor

Original assessment: 27th August 2004

Response assessment: 30th March 2005

Response assessment 10th November 2005

Response assessment: 14th March 2006

Response assessment: 14th June 2006

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

INTRODUCTION

These are National Abridged generic applications for MA for OTC Ibuprofen Paediatric Suspension for 100mg/5ml and are submitted under 10.1 [formerly Article 10.1(a)(iii)] of Directive 2001/83/EC. Essential similarity to Junifen Suspension 100mg/5ml (PL 00327/0077, Crookes Healthcare Ltd), which was first licensed >10 years ago (Aug 1993) is claimed. The proposed legal status is P (OTC - pharmacy only). Subsequent MRP is not planned. It is proposed that Ibuprofen Paediatric Suspension (PL 12063/0060) be on sale in pharmacies only (P legal status) and Ibuprofen Paediatric Suspension or Ibuprofen Suspension for Children (PL 12063/0061) be on general sale (legal status GSL).

Preparations containing ibuprofen have been available in the UK since 1966 and the Clinical Summary reviews the use of ibuprofen in children. The application is supported by a single bioequivalence study (vs. Nurofen for Children 100mg/5ml). This documentation for this study was supplied with Module 3; no Module 5 was submitted.

The Clinical Expert is appropriately medically qualified.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Introduction

The PK of ibuprofen is well understood and has been reviewed in the Clinical Summary.

In support of this generic application, a single bioequivalence study has been conducted to prove that the proposed ibuprofen suspension 100mg/5ml (Wrafton Laboratories Ltd) and Nurofen for Children (Crookes Healthcare; PL 00327/0085). The batch of Ibuprofen 100mg/5ml suspension is at least 10% of the proposed maximum batch size.

Methods

Study SC00403 Title: A single-dose, randomised, crossover study to compare the absorption of two formulations of ibuprofen suspension in healthy male and female volunteers

The objective of this study was to evaluate the PK characteristics and relative bioavailability profile of the proposed ibuprofen suspension (Wrafton Laboratories Ltd)- Test product - compared to the UK licensed comparator Nurofen for Children (Crookes Healthcare Ltd; PL 00327/0085) – reference product.

The study was carried-out in 21 healthy male and female adult volunteers (20 of whom completed the study). As the PK of ibuprofen is independent of age in the proposed dose range, extrapolation from findings in adults is accepted.

The dose given was 400mg/20ml. Samples were taken predose (0 hours) and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 5, 7, 9 and 12 hours post dose. An adequate period of at least 48 hours was used between treatments.

- **Analytical methods**

The methods used were satisfactory.

- **Pharmacokinetic data analysis**

The primary parameters were C_{max}, AUC_{0-t} and extrapolated AUC_{0-∞}. Secondary parameters were t_{max}, t_{1/2}, MRT (mean residence time – extrapolated area under the concentration vs. time curve) and k_{el} (terminal elimination rate constant). Safety was also monitored using standard methodology.

- **Statistical analysis**

PK parameters were determined in a model-independent way. ANOVA and 90% CIs were calculated for the mean ratios of AUC and C_{max} after log transformation. Parametric testing was used when data were normally distributed; non-parametric testing when not normally distributed. A comparison of t_{max} was done through descriptive statistics. The acceptance range for the 90% C is to establish bioequivalence of Test: Reference formulations was the standard 80-125%, using log transformed data of the primary endpoints, as per the CPMP Guideline.

Bioequivalence was determined using the 90% confidence interval of the relative mean AUC 0-t, AUC_∞ and C_{max} of the test to reference formulation which should be 80% to 125%. The results are presented in section II.1.3, which follows.

Absorption

- **Bioequivalence**

The mean t_{max} values for Ibuprofen 100mg/5ml suspension (Test product) and Nurofen for Children 100mg/5ml suspension (Reference product) were 1.10 and 0.86 hours respectively. The results for the primary parameters are tabulated in Tables 1 and 2.

Table 1. Summary statistics for the primary parameters Test vs Reference

Variable	Arithmetic mean		Minimum		maximum	
	Test	Reference	Test	Reference	Test	Reference
C _{max} (µg/ml)	37.80 ± 7.18	38.96 ± 7.13	18.88	26.01	49.46	52.72
AUC _{0-t} (µg/ml.h)	120.42 ± 25.31	117.23 ± 20.17	72.38	78.73	195.68	163.34
AUC _{0-∞} (µg/ml.h)	123.49 ± 26.67	119.92 ± 20.82	74.76	80.28	205.16	166.17

Table 2. CIs and point estimates for the primary parameters Test vs Ref

Variable	Geometric mean		90% CI	Point estimate
	Test	Reference		
C _{max} (µg/ml)	37.06	38.32	91.40%-102.30%	96.70%
AUC _{0-t} (µg/ml.h)	118.04	115.51	96.64%-108.50%	102.19%
AUC _{0-∞} (µg/ml.h)	120.96	118.13	96.97%-108.13%	102.40%

As can be seen from the tables, Study SC00403 showed that for the test suspension (ibuprofen suspension, Wrafton Laboratories) and the reference suspension (Nurofen for Children, Crookes) were as follows:

- Mean C_{max} for the Test suspension was 38.32 µg/ml and for the Reference suspension was 38.32µg/ml (point estimate 96.7% and 90% CIs 91.4 – 102.3%).
- Mean AUC_{0-t} was 118.04µg/ml.h for the Test suspension cf. 115.51µg/ml.h for the rReference (point estimate 102.19%; 90% CIs 96.64-108.50%).
- Mean extrapolated AUC_{0-∞} was 120.96µg/ml.h for the test and 118.13µg/ml.h for the Reference product (point estimate 102.40%; 90% CI 96.97 – 108.13%).

These results are well within the acceptance criteria and the products may, therefore, be considered bioequivalent. Comparison of the additional parameters revealed the following:

- The median (Min-Max) t_{max} values for Test and Reference products were 0.75h (0.5-3.0h) and 0.75h (0.50-2.0h), respectively. The statistically significant treatment effect (p=0.0324) was observed, indicating a longer t_{max} for the Test product.
- The geometric means calculated for t_{1/2} were 2.22h and 2.06h, respectively for Test and Reference products.
- The geometric means calculated for MRT were 3.30h and 3.13h, respectively for the Test and Reference products. A low intra-individual CV of 7.04% resulted in a small least significant difference value and consequently the statistically significant treatment effect (0.0266) was observed, indicating a longer MRT for the Test product.

Assessor's overall conclusions on pharmacokinetics

Study SC00403 has established that the rate and extent of absorption of ibuprofen from the proposed formulation is bioequivalent to that of the reference product, Nurofen for Children. Although the study was conducted in adults, a study in children would not be ethical given that there is no reason to believe the data cannot be extrapolated from adults to the target population. The Applicant compared the proposed formulation with Nurofen, presumably as this is the market leader and Junifen, with which essential similarity is claimed, is no longer marketed. The Assessor has discussed this with the pharmaceutical assessor and unit manager and this approach is considered to be satisfactory from a regulatory perspective.

Pharmacodynamics

ATC Code M01AE –propionic acid derivatives.

The PD actions of ibuprofen in both adults and children are well understood. No new data have been submitted and none are required for this type of application.

CLINICAL EFFICACY

No new data have been submitted and none are required for this type of application. The efficacy of ibuprofen in the proposed indications is well-recognised and has been adequately reviewed in the Clinical Summary.

CLINICAL SAFETY

No new data have been submitted and none are required for this type of application. The safety profile of ibuprofen in both adults and children is well established and has been reviewed in the Clinical Summary. There are no new safety concerns arising from this review or from the Phase I Bioequivalence study. In this study 6 AEs were reported in 4 volunteers – three reports of headache, one of vomiting, one of dizziness and one of urticaria. These are consistent with events seen in Phase I studies and no formulation events can be deduced from these results. There were no SAEs or other safety findings.

SPC/PIL/Label

Satisfactory.

CONCLUSIONS

Given the demonstration of bioequivalence with Nurofen for Children, the current brand leader (Junifen being no longer marketed) MA may be granted.

Medical Assessor
October 2004
Updated 2006

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Paramed Ibuprofen For Children 100mg/5ml Oral Suspension and Oral Suspension Sachets (PL 12063/0060-1) 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 have been supplied with these applications and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Paramed Ibuprofen For Children 100mg/5ml Oral Suspension and Oral Suspension Sachets (PL 12063/0060-1) and the originator product Junifen suspension 100mg/5ml (PL 00327/0077).

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Junifen suspension 100mg/5ml (PL 00327/0077).

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's products and the innovator products are interchangeable. Clinical experience with Ibuprofen is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

**PARAMED IBUPROFEN FOR CHILDREN 100 MG/5 ML
ORAL SUSPENSION & ORAL SUSPENSION SACHETS**

PL 12063/0060-1

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 27/02/2004
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 12/03/2004
3	Following assessment of the application the MHRA requested further information relating to the dossier on 23/08/2004, 14/10/2004, 02/11/2004, 17/06/2004, 07/12/2005 and 14/03/2006
4	The applicant responded to the MHRA's requests, providing further information relating to the dossier on 26/08/2004, 18/03/2004, 12/10/2005, 13/02/2006, 14/02/2006, 05/05/2006, 12/05/2006 and 12/06/2006,
5	The application was determined on 07/09/2006

**PARAMED IBUPROFEN FOR CHILDREN 100 MG/5 ML
ORAL SUSPENSION & ORAL SUSPENSION SACHETS**

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STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

**PARAMED IBUPROFEN FOR CHILDREN 100 MG/5 ML ORAL SUSPENSION
PL 12063/0060**

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Paramed Ibuprofen for Children 100 mg/5 ml Oral Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient: Ibuprofen 100 mg/5 ml (equivalent to 2.0% w/v).

This product also contains the excipient maltitol liquid, see section 4.3.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension

Opaque, white to off-white viscous suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the fast and effective reduction of fever, including post immunisation pyrexia, cold and flu symptoms, and the fast and effective relief of mild to moderate pain, such as sore throat, teething pain, toothache, earache, headache, minor aches and sprains.

4.2 Posology and method of administration

For oral administration and short term use only

Shake the bottle well before use.

For pain and fever:

For children weighing 5 kg or more, the daily dosage of the suspension is 20 mg/kg bodyweight in divided doses. Using the spoon provided this can be achieved as follows:

Infants 3 – 6 months (weighing over 5 kg): One 2.5 ml dose may be taken 3 times in 24 hours.

Infants 6 – 12 months: One 2.5 ml dose may be taken 3 to 4 times in 24 hours.

Children 1 – 3 years: One 5 ml dose may be taken 3 times in 24 hours.

Children 4 – 6 years: 7.5 ml dose (5 ml + 2.5 ml spoonful) may be taken 3 times in 24 hours.

Children 7 – 9 years: 10 ml dose. Two 5 ml spoonfuls may be taken 3 times in 24 hours.

Children 10 – 12 years: 15 ml dose. Three 5 ml spoonfuls may be taken 3 times in 24 hours.

Not suitable for children under 3 months of age, or for children weighing less than 5 kg, unless advised by your doctor.

Leave at least 4 hours between doses.

For post immunisation pyrexia:

One 2.5 ml dose followed by one further 2.5 ml dose 6 hours later if necessary. No more than two 2.5 ml doses in 24 hours. If the fever is not reduced, consult your doctor.

4.3 Contraindications

Hypersensitivity to ibuprofen or any of the constituents of the product

Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema, or urticaria) associated with aspirin or other non-steroidal anti-inflammatory drugs.

Patients with a history of, or existing peptic ulceration

History of upper gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

Use with concomitant NSAIDs including cyclo-oxygenase-2 specific inhibitors (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Severe hepatic failure, renal failure or heart failure (see Section 4.4 Special warnings and precautions for use)

Last trimester of pregnancy (see Section 4.6 Pregnancy and lactation)

Each 5 ml spoonful contains 2 g of maltitol liquid. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.4 Special warnings and precautions for use

Bronchospasm 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 minimum effective dose for the shortest possible duration.

The elderly are at increased risk of the serious consequences of adverse reactions.

Systemic lupus erythematosus and mixed connective tissue disease - increased risk of aseptic meningitis (See section 4.8 Undesirable effects).

Chronic inflammatory intestinal disease (ulcerative colitis, Crohn's disease) – as these conditions may be exacerbated (See section 4.8 Undesirable effects).

Hypertension and/or cardiac impairment as renal function may deteriorate and/or fluid retention occur.

Renal impairment as renal function may further deteriorate (See section 4.3 Contraindications and Section 4.8 Undesirable effects).

Hepatic dysfunction (See section 4.3 contraindications and Section 4.8 undesirable effects).

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.

Gastrointestinal 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 gastrointestinal events.

Patients with a history of gastrointestinal toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial 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 interaction with other medicinal products and other forms of interaction).

When gastrointestinal bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn.

The label will include:

Please read the enclosed leaflet carefully.

Do not let your child take this medicine if they:

- are under 3 months old, or weigh less than 5 kg, unless advised by your doctor
- are allergic to ibuprofen or any of the other ingredients, aspirin or other related painkillers
- have or have ever had a stomach ulcer, perforation or bleeding
- are intolerant to some sugars
- are taking other NSAID painkillers, or aspirin, with a daily dose above 75 mg.

Consult your doctor or pharmacist if your child has asthma, or heart, liver, kidney or bowel problems, or is receiving any other regular treatment.

Pregnant women considering taking this medicinal product should consult their doctor before use.

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

For children under 6 months, if the symptoms persist for more than 24 hours (3 doses) or worsen, consult your doctor.

Warning – Do not exceed the stated dose.

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

Not suitable for children under 3 months of age or weighing less than 5 kg, unless advised by your doctor.

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 75mg daily) has been advised by a doctor, as this may increase the risk of adverse reactions (See section 4.3 Contraindications)

Other NSAIDs:

As these may increase the risk of adverse effects (See section 4.3 Contraindications)

Ibuprofen should be used with caution in combination with:

Anticoagulants:

NSAIDs may enhance the effects of anti-coagulants, such as warfarin (See section 4.4 Special warnings and precautions for use).

Antihypertensives and diuretics:

NSAIDs may diminish the effect of these drugs.

Corticosteroids:

May increase the risk of adverse reactions in 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 an increase in plasma methotrexate.

Zidovudine:

There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

4.6 Pregnancy and lactation

Children under 12 are unlikely to become pregnant or breast feed, however, whilst no teratogenic effects have been demonstrated in animal studies, the use of the suspension should be avoided if possible during the first six 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 duration of labour increased with an increased bleeding tendency in both mother and child (see Section 4.3 – contraindications).

In limited studies, ibuprofen appears in breast milk in very low concentration 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 and 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 long-term treatment, additional adverse effects may occur.

Hypersensitivity reactions:

Uncommon:

Hypersensitivity reactions with urticaria and pruritus

Very rare:

Severe hypersensitivity reactions. Symptoms could be: facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock).

Exacerbation of asthma and bronchospasm

Gastrointestinal:

Uncommon:

Abdominal pain, nausea and dyspepsia

Rare:

Diarrhoea, flatulence, constipation and vomiting

Very rare:

Peptic ulcer, perforation or gastrointestinal haemorrhage, sometimes fatal, particularly in the elderly. Exacerbation of ulcerative colitis and Crohn's disease (See section 4.4)

Nervous System:

Uncommon:

Headache

Renal:

Very rare:

Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema.

Hepatic:

Very rare:

Liver disorders

Haematological:

Very rare:

Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.

Skin:

Uncommon:

Various skin rashes

Very rare:

Severe forms of skin reactions such as erythema multiforme and epidermal necrolysis can occur.

Immune System:

In patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed (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 drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In

serious poisoning metabolic acidosis may occur and the prothrombin time/ INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur. Exacerbation of asthma is possible in asthmatics.

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

Pharmacotherapeutic group: Propionic acid derivatives
ATC code: M01AE01

Ibuprofen is a propionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. It has analgesic, antipyretic and anti-inflammatory properties.

Furthermore, ibuprofen reversibly inhibits platelet aggregation.

Ibuprofen has been shown to have an onset of both analgesic and antipyretic action within 30 minutes.

5.2 Pharmacokinetic properties

Ibuprofen is rapidly absorbed following administration and is rapidly distributed throughout the whole body. The excretion is both 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 – 2 hours. These times may vary with different dosage forms.

The half life of ibuprofen is about two hours.

In limited studies, ibuprofen appears in the breast milk in very low concentrations.

5.3 Preclinical safety data

There are no preclinical safety data of relevance to the consumer.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maltitol Liquid
Glycerol
Xanthan Gum
Sodium Benzoate
Sodium Cyclamate
Citric Acid
Orange Flavour
Acesulfame Potassium
Polysorbate 80
Disodium Edetate
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

There are no special storage instructions.

6.5 Nature and contents of container

Amber-coloured polyethylene terephthalate (PET) bottle with a child-resistant, high-density polyethylene closure fitted with a polypropylene inner layer and insert comprising folding boxboard/paper/aluminium foil/wax disc. The bottle contains 100 ml of product. A double-ended spoon with measures of 2.5 ml and 5 ml is provided.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Wrafton Laboratories Limited
Wrafton
Braunton
North Devon
EX33 2DL

8. MARKETING AUTHORISATION NUMBER(S)

PL 12063/0060.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/09/2006

10 DATE OF REVISION OF THE TEXT

07/09/2006

**PARAMED IBUPROFEN FOR CHILDREN 100 MG/5 ML ORAL SUSPENSION
PL 12063/0061**

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Paramed Ibuprofen for Children 100 mg/5 ml Oral Suspension Sachets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient: Ibuprofen 100 mg/5 ml (equivalent to 2.0% w/v).

This product also contains the excipient maltitol liquid, see section 4.3.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension

Opaque, white to off-white viscous suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the fast and effective reduction of fever, including post immunisation pyrexia, cold and flu symptoms, and the fast and effective relief of mild to moderate pain, such as sore throat, teething pain, toothache, headache, minor aches and sprains.

4.2 Posology and method of administration

For oral administration and short term use only

Squeeze the sachet to aid mixing.

For pain and fever:

For children weighing 5 kg or more, the daily dosage of the suspension is 20 mg/kg bodyweight in divided doses. Using the spoon provided this can be achieved as follows:

Infants 3 – 6 months (weighing over 5 kg): One 2.5 ml dose may be taken 3 times in 24 hours.

Infants 6 – 12 months: One 2.5 ml dose may be taken 3 to 4 times in 24 hours.

Children 1 – 3 years: One 5 ml dose may be taken 3 times in 24 hours.

Children 4 – 6 years: 7.5 ml dose (5 ml + 2.5 ml spoonful) may be taken 3 times in 24 hours.

Children 7 – 12 years: 10 ml dose Two 5 ml spoonfuls may be taken 3 times in 24 hours.

Not suitable for children under 3 months of age or for children weighing less than 5 kg. Leave at least 4 hours between doses.

For post immunisation pyrexia:

One 2.5 ml dose followed by one further 2.5 ml dose 6 hours later if necessary. No more than two 2.5 ml doses in 24 hours. If the fever is not reduced, consult your doctor.

4.3 Contraindications

Hypersensitivity to ibuprofen or any of the constituents of the product

Patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema, or urticaria) associated with aspirin or other non-steroidal anti-inflammatory drugs.

Patients with a history of, or existing peptic ulceration

History of upper gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

Use with concomitant NSAIDs including cyclo-oxygenase-2 specific inhibitors (See Section 4.5 Interaction with other medicinal products and other forms of interaction).

Severe hepatic failure, renal failure or heart failure (See Section 4.4 Special warnings and precautions for use)

Last trimester of pregnancy (See Section 4.6 Pregnancy and lactation)

Each 5ml spoonful contains 2g of maltitol liquid. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.4 Special warnings and precautions for use

Bronchospasm 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 minimum effective dose for the shortest possible duration.

The elderly are at increased risk of the serious consequences of adverse reactions.

Systemic lupus erythematosus and mixed connective tissue disease – increased risk of aseptic meningitis (See Section 4.8 Undesirable effects).

Chronic inflammatory intestinal disease (ulcerative colitis, Crohn's disease) – as these conditions may be exacerbated (See Section 4.8 Undesirable effects).

Hypertension and/or cardiac impairment as renal function may deteriorate and/or fluid retention occur.

Renal impairment as renal function may further deteriorate (See Section 4.3 Contraindications and Section 4.8 Undesirable effects).

Hepatic dysfunction (See Section 4.3 contraindications and Section 4.8 undesirable effects)

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.

Gastrointestinal 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 gastrointestinal events.

Patients with a history of gastrointestinal toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial 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 interaction with other medicinal products and other forms of interaction).

When gastrointestinal bleeding or ulceration occurs in patients receiving ibuprofen, the treatment should be withdrawn.

The label will include:

Please read the enclosed leaflet carefully.

Do not let your child take this medicine if they:

- are under 3 months old, or weigh less than 5 kg
- are allergic to ibuprofen or any of the other ingredients, aspirin or other related painkillers
- have or have ever had a stomach ulcer, perforation or bleeding
- are intolerant to some sugars
- are taking other NSAID painkillers, or aspirin, with a daily dose above 75 mg

Consult your doctor or pharmacist if your child has asthma, or heart, liver, kidney or bowel problems, or is receiving any regular treatment.

Pregnant women considering taking this medicinal product should consult their doctor before use.

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

For children under 6 months, if the symptoms persist for more than 24 hours (3 doses) or worsen, consult your doctor.

Warning – Do not exceed the stated dose.

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

Not suitable for children under 3 months of age or weighing less than 5 kg.

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 75mg daily) has been advised by a doctor, as this may increase the risk of adverse reactions (See Section 4.3 contraindications)

Other NSAIDs:

As these may increase the risk of adverse effects (See Section 4.3 contraindications)

Ibuprofen should be used with caution in combination with:

Anticoagulants:

NSAIDs may enhance the effects of anti-coagulants, such as warfarin (See Section 4.4 special warnings and precautions for use).

Antihypertensives and diuretics:

NSAIDs may diminish the effect of these drugs.

Corticosteroids:

May increase the risk of adverse reactions in 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 an increase in plasma methotrexate.

Zidovudine:

There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

4.6 Pregnancy and lactation

Children under 12 are unlikely to become pregnant or breast feed, however, whilst no teratogenic effects have been demonstrated in animal studies, the use of the suspension should be avoided if possible during the first six 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 contraindications).

In limited studies, ibuprofen appears in the breast milk in very low concentration 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 and 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 long-term treatment, additional adverse effects may occur.

Hypersensitivity reactions:

Uncommon:

Hypersensitivity reactions with urticaria and pruritus

Very rare:

Severe hypersensitivity reactions. Symptoms could be: facial, tongue and laryngeal swelling, dyspnoea, tachycardia, hypotension, (anaphylaxis, angioedema or severe shock).

Exacerbation of asthma and bronchospasm

Gastrointestinal:

Uncommon:

Abdominal pain, nausea and dyspepsia

Rare:

Diarrhoea, flatulence, constipation and vomiting

Very rare:

Peptic ulcer, perforation or gastrointestinal haemorrhage, sometimes fatal, particularly in the elderly. Exacerbation of ulcerative colitis and Crohn's disease (See section 4.4)

Nervous System:

Uncommon:

Headache

Renal:

Very rare:

Acute renal failure, papillary necrosis, especially in long-term use, associated with increased serum urea and oedema.

Hepatic:

Very rare:

Liver disorders

Haematological:

Very rare:

Haematopoietic disorders (anaemia, leucopenia, thrombocytopenia, pancytopenia, agranulocytosis). First signs are: fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising.

Skin:

Uncommon:

Various skin rashes

Very rare:

Severe forms of skin reactions such as erythema multiforme and epidermal necrolysis can occur.

Immune System:

In patients with existing auto-immune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) during treatment with ibuprofen, single cases of symptoms of aseptic meningitis, such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed (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 drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning metabolic acidosis may occur and the prothrombin time/ INR may be prolonged, probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur. Exacerbation of asthma is possible in asthmatics.

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

Pharmacotherapeutic group: Propionic acid derivatives
ATC code: M01AE01

MHRA PAR Paramed Ibuprofen for Children 100 mg/5 ml Oral Suspension & Oral Suspension Sachets PL 12063/0060-1

Ibuprofen is a propionic acid derivative NSAID that has demonstrated its efficacy by inhibition of prostaglandin synthesis. It has analgesic, antipyretic and anti-inflammatory properties.

Furthermore, ibuprofen reversibly inhibits platelet aggregation. Ibuprofen has been shown to have an onset of both analgesic and antipyretic action within 30 minutes.

5.2 Pharmacokinetic properties

Ibuprofen is rapidly absorbed following administration and is rapidly distributed throughout the whole body. The excretion is both 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 – 2 hours. These times may vary with different dosage forms.

The half life of ibuprofen is about two hours.

In limited studies, ibuprofen appears in the breast milk in very low concentrations.

5.3 Preclinical safety data

There are no preclinical safety data of relevance to the consumer.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maltitol Liquid
Glycerol
Xanthan Gum
Sodium Benzoate
Sodium Cyclamate
Citric Acid
Orange Flavour
Acesulfame Potassium
Polysorbate 80
Disodium Edetate
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

The suspension is packed in laminate sachets consisting of Surlyn® ionomer (product contact material)/low density polyethylene/8 micron aluminium/paper.

Each sachet contains 5 ml of the suspension.

Pack sizes of 8 or 16 sachets in a cardboard carton.

A double-ended spoon with measures of 2.5 ml and 5 ml is provided.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Wrafton Laboratories Limited
Wrafton
Braunton
North Devon
EX33 2DL

8. MARKETING AUTHORISATION NUMBER(S)

PL 12063/0061.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/09/2006

10. DATE OF REVISION OF THE TEXT

07/09/2006

PARAMED IBUPROFEN FOR CHILDREN 100 MG/5 ML ORAL SUSPENSION
PL 12063/0060
PRODUCT INFORMATION LEAFLET



IBUPROFEN FOR CHILDREN 100mg/5ml ORAL SUSPENSION **100ml BOTTLE**

PATIENT INFORMATION LEAFLET

Read all of this leaflet carefully because it contains important information for you. This medicine is available without prescription. Nevertheless, you still need to use this product carefully to get the best results from it. Keep this leaflet, you may need to read it again. Ask your pharmacist if you need more information or advice. You must see a doctor if your symptoms worsen or do not improve.

What is Paramed® Ibuprofen For Children 100mg/5ml Oral Suspension?

The bottle contains 100 ml of an off-white thick suspension containing the active ingredient ibuprofen which can be given to your child by mouth. Each 5 ml of suspension contains 100 mg of ibuprofen.

Also contains: Purified Water, Maltitol Liquid, Glycerol, Xanthan Gum, Sodium Benzoate, Sodium Cyclamate, Citric Acid, Orange Flavour, Acesulfame Potassium, Polysorbate 80 and Sodium Edetate.

Marketing Authorisation Holder and Manufacturer:
Wratton Laboratories Ltd., Wratton, Braunton, Devon, EX39 2DL UK.

What is it used for?

Ibuprofen belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). This medicine contains the active ingredient, ibuprofen which acts to reduce fever, including post-immunisation fever, relieves cold and flu symptoms, and provides relief of mild to moderate pain, such as sore throat, teething pain, toothache, earache, headache, minor aches and sprains. This suspension may be used to relieve these symptoms in babies and children aged from 3 months.

Do not give this medicine to your child if they:

- are under 3 months old or weigh less than 5kg, unless advised by your doctor.
- have a history of asthma, rashes, swellings or other allergic conditions associated with aspirin or other similar medicines.

- have, or have ever had in the past, a stomach ulcer, perforation or bleeding or other serious stomach disorder.
- are allergic to ibuprofen or any other ingredient of the product, aspirin or other related painkillers.
- are taking other NSAID painkillers, or aspirin with a daily dose above 75mg.
- have developed asthma, rhinitis, angioedema or hives (urticaria) after taking aspirin, ibuprofen or other NSAIDs.

Pregnant women should consult their doctor before taking ibuprofen.

Before your child takes this medicine:

Consult your doctor or pharmacist before using this product if your child has asthma, or has heart, liver, kidney or bowel problems. If your child is on a low dose aspirin (up to 75mg daily) speak to your doctor or pharmacist before giving this suspension. Each 5 ml spoonful of this medicine contains 2 g of Maltitol liquid. If your child has been told by their doctor that they have an intolerance to some sugars, contact a doctor before your child takes this medicine.

You should also consult your doctor if your child is taking other medicines such as:

- Aspirin or other Non-Steroidal Anti-inflammatory Drugs (NSAIDs).
- Drugs which thin the blood (oral anti-coagulants).
- Drugs for high blood pressure (anti-hypertensives).
- Water tablets (diuretics).
- Lithium or methotrexate.
- Corticosteroids ('steroids').
- Zidovudine (HIV treatment).

Ibuprofen belongs to a group of medicines which may impair fertility in women. This effect is reversible on stopping the medicine. It is unlikely that ibuprofen, used occasionally, will affect a woman's chances of becoming pregnant, however, she should consult her doctor before taking this medicine if she is having problems becoming pregnant.

How should this suspension be used?

For oral use. Use the measuring spoon provided to carefully measure out the required dose as explained below. The double-ended spoon has two measures of 2.5 ml and 5 ml. Shake the bottle well before use.

DOSAGE

For children weighing 5 kg or more, the daily dosage of this suspension is 20 mg/kg bodyweight in divided doses. Leave at least 4 hours between doses. Using the spoon provided this can be achieved as follows:

FOR PAIN & FEVER

Infants 3 - 6 months (weighing over 5kg):

One 2.5ml dose may be taken 3 times in 24 hours.

Infants 6 - 12 months:

One 2.5ml dose may be taken 3 to 4 times in 24 hours.

Children 1 - 3 years:

One 5ml dose may be taken 3 times in 24 hours.

Children 4 - 6 years:

7.5ml dose (5 ml + 2.5ml spoonful) may be taken 3 times in 24 hours.

Children 7 - 9 years:

10ml dose. Two 5ml spoonfuls may be taken 3 times in 24 hours.

Children 10 - 12 years:

15ml dose. Three 5ml spoonfuls may be taken 3 times in 24 hours.

FOR POST IMMUNISATION FEVER

One 2.5 ml dose followed by one further 2.5 ml dose 6 hours later if necessary. No more than two 2.5 ml doses in 24 hours. If the fever is not reduced, consult your doctor.

Not suitable for children under 3 months of age or weighing less than 5kg, unless advised by your doctor. **For short term use only.** Do not give to infants aged 3 - 6 months for more than 24 hours, or children over 6 months for more than 3 days. If symptoms persist for longer than these times, or worsen, consult your doctor.

Warning: Do not exceed the stated dose.

If your child takes too much of this suspension, medical advice should be sought immediately.

Possible side effects

If your child develops a side-effect, or you have any concerns, stop giving this medicine and talk to your doctor or pharmacist as soon as possible:

The most common side-effects are:

- A mild laxative effect.
- Stomach discomfort.

Rare side-effects are:

- Nausea, stomach pain.
- Rash, itching, worsening of asthma, unexplained wheezing or shortness of breath.

More rarely:

- Facial swelling **SEEK MEDICAL HELP IMMEDIATELY IF THIS HAPPENS** (It may be a rare but serious, allergic reaction.)
- Black, tarry stools, stomach ulcers or bleeding.
- Skin peeling, easy bruising.

If any of the following occur at any time during treatment STOP GIVING this medicine and seek immediate medical help:

- Passage of blood in the faeces (stools/motions).
- Passage of black tarry stools.
- Vomiting of blood or dark particles which look like coffee grounds.

STOP GIVING the medicine and tell your doctor if your child develops:

- Indigestion or heartburn.
- Abdominal pains (pains in the stomach) or other abdominal symptoms.

Instructions for storage:

There are no special storage instructions.

KEEP ALL MEDICINES OUT OF THE REACH AND SIGHT OF CHILDREN.

Do not use the suspension after the date shown on the pack.

PL 12063/0060

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Text revised April 2006

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**PARAMED IBUPROFEN FOR CHILDREN 100 MG/5 ML ORAL SUSPENSION SACHETS
PL 12063/0061
PRODUCT INFORMATION LEAFLET**



IBUPROFEN FOR CHILDREN 100mg/5ml ORAL SUSPENSION SACHETS

PATIENT INFORMATION LEAFLET

Read all of this leaflet carefully because it contains important information for you. This medicine is available without prescription. Nevertheless, you still need to use this product carefully to get the best results from it. Keep this leaflet, you may need to read it again. Ask your pharmacist if you need more information or advice. You must see a doctor if your symptoms worsen or do not improve.

What Are Paramed® Ibuprofen For Children 100mg/5ml Oral Suspension Sachets?

The sachet contains 5 ml of an off-white thick suspension containing the active ingredient ibuprofen which can be given to your child by mouth. This pack contains 8 or 16 sachets, each of 5 ml.

Also contains: Purified Water, Maltitol Liquid, Glycerol, Xanthan Gum, Sodium Benzoate, Sodium Cyclamate, Citric Acid, Orange Flavour, Acesulfame Potassium, Polysorbate 80 and Sodium Edetate.

Marketing Authorisation Holder and Manufacturer:
Wrafton Laboratories Ltd., Wrafton, Braunton, Devon,
EX33 2DL UK.

What is it used for?

Ibuprofen belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). This medicine contains the active ingredient, ibuprofen which acts to reduce fever, including post-immunisation fever, relieves cold and flu symptoms, and provides relief of mild to moderate pain, such as sore throat, teething pain, toothache, headache, minor aches and sprains. This suspension may be used to relieve these symptoms in babies and children aged from 3 months.

Do not give this medicine to your child if they:

- are under 3 months of age or weigh less than 5kg
- have a history of asthma, rashes, swellings or other allergic conditions associated with aspirin or other similar medicines

- have, or have ever had in the past, a stomach ulcer, perforation or bleeding or other serious stomach disorder
- are allergic to ibuprofen or any other ingredient of the product, aspirin or other related painkillers
- are taking other NSAID painkillers, or aspirin with a daily dose above 75mg
- have developed asthma, rhinitis, angioedema or hives (urticaria) after taking aspirin, ibuprofen or other NSAIDs

Pregnant women should consult their doctor before taking ibuprofen.

Before your child takes this medicine:

Consult your doctor or pharmacist before using this product if your child has asthma, or has heart, liver, kidney or bowel problems. If your child is on a low dose aspirin (up to 75mg daily) speak to your doctor or pharmacist before giving this suspension. Each 5 ml spoonful of this medicine contains 2 g of Maltitol liquid. If your child has been told by their doctor that they have an intolerance to some sugars, contact a doctor before your child takes this medicine.

You should also consult your doctor if your child is taking other medicines such as:

- Aspirin or other Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).
- Drugs which thin the blood (oral anti-coagulants).
- Drugs for high blood pressure (anti-hypertensives).
- Water tablets (diuretics).
- Lithium or methotrexate.
- Corticosteroids ("steroids").
- Zidovudine (HIV treatment).

Ibuprofen belongs to a group of medicines which may impair fertility in women. This effect is reversible on stopping the medicine. It is unlikely that ibuprofen, used occasionally, will affect a woman's chances of becoming pregnant, however, she should consult her doctor before taking this medicine if she is having problems becoming pregnant.

How should this suspension be used?

For oral use. Carefully squeeze the sachet to aid mixing prior to opening. Open the sachet and use the measuring spoon provided to carefully measure out the required dose as explained below. The double-ended spoon has two measures of 2.5 ml and 5 ml.

DOSAGE

For children weighing 5 kg or more, the daily dosage of this suspension is 20 mg/kg bodyweight in divided doses. Leave at least 4 hours between doses. Using the spoon provided this can be achieved as follows:

FOR PAIN & FEVER**Infants 3 - 6 months (weighing over 5kg):**

One 2.5ml dose may be taken 3 times in 24 hours.

Infants 6 - 12 months:

One 2.5ml dose may be taken 3 to 4 times in 24 hours.

Children 1 - 3 years:

One 5ml dose may be taken 3 times in 24 hours.

Children 4 - 6 years:

7.5ml dose (5 ml + 2.5ml spoonful) may be taken 3 times in 24 hours.

Children 7 - 12 years:

10ml dose. Two 5ml spoonfuls may be taken 3 times in 24 hours.

FOR POST IMMUNISATION FEVER

One 2.5 ml dose followed by one further 2.5 ml dose 6 hours later if necessary. No more than two 2.5 ml doses in 24 hours. If the fever is not reduced, consult your doctor.

Not suitable for children under 3 months of age or weighing less than 5kg.

For short term use only. Do not give to infants aged 3 - 6 months for more than 24 hours, or children over 6 months for more than 3 days. If symptoms persist for longer than these times, or worsen, consult your doctor.

Warning: Do not exceed the stated dose.

If your child takes too much of this suspension, medical advice should be sought immediately.

Possible side effects

If your child develops a side-effect, or you have any concerns, stop giving this medicine and talk to your doctor or pharmacist as soon as possible:

The most common side-effects are:

- A mild laxative effect.
- Stomach discomfort.

Rare side-effects are:

- Nausea, stomach pain.
- Rash, itching, worsening of asthma, unexplained wheezing or shortness of breath.

More rarely:

- Facial swelling **SEEK MEDICAL HELP IMMEDIATELY IF THIS HAPPENS** [it may be a rare but serious, allergic reaction.]
- Black, tarry stools, stomach ulcers or bleeding.
- Skin peeling, easy bruising.

If any of the following occur at any time during treatment STOP GIVING this medicine and seek immediate medical help:

- Passage of blood in the faeces (stools/motions).
- Passage of black tarry stools.
- Vomiting of blood or dark particles which look like coffee grounds.

STOP GIVING the medicine and tell your doctor if your child develops:

- Indigestion or heartburn.
- Abdominal pains (pains in the stomach) or other abdominal symptoms.

Instructions for storage:

Do not store above 25°C.

KEEP ALL MEDICINES OUT OF THE REACH AND SIGHT OF CHILDREN.

Do not use the suspension after the date shown on the pack.

PL 12063/0061

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Text revised April 2006

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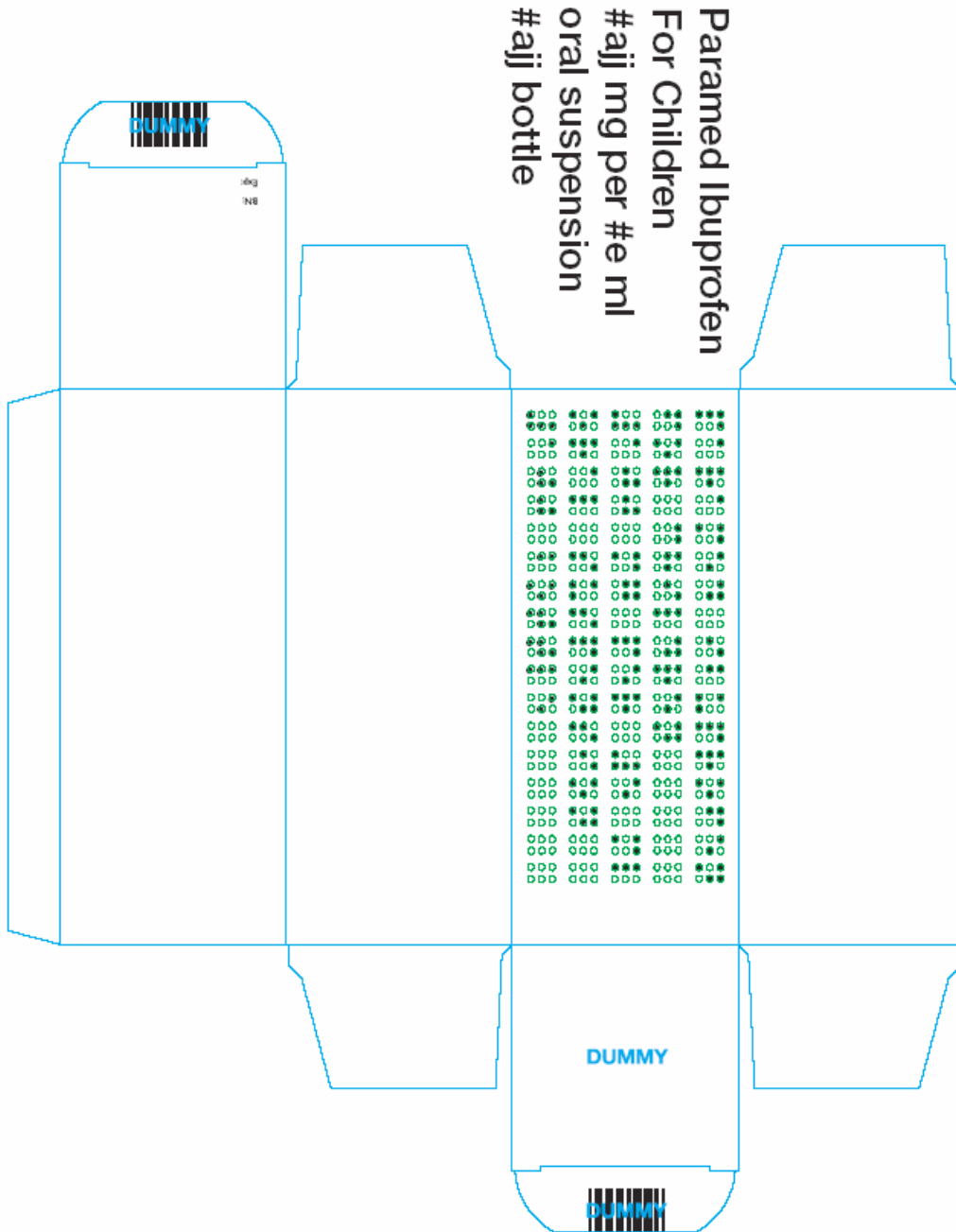
**PARAMED IBUPROFEN FOR CHILDREN 100 MG/5 ML ORAL SUSPENSION
PL 12063/0060**

LABEL

<p>Reduces fever, including post-immunisation fever. Relieves cold & flu symptoms and mild to moderate pain including sore throat, teething pain, toothache, earache, headache, minor aches & sprains.</p> <p>DIRECTIONS FOR USE For oral use. Shake bottle well and use measuring spoon provided.</p> <p>DOSAGE For children from 3 months. Not suitable for children under 3 months of age or weighing less than 5kg, unless advised by your doctor. Leave at least 4 hours between doses.</p> <p>For pain & fever:</p> <table border="1"> <thead> <tr> <th>Age</th> <th>Dose</th> <th>Frequency</th> </tr> </thead> <tbody> <tr> <td>3 – 6 months (+ over 5kg):</td> <td>2.5 ml</td> <td>3 times / day</td> </tr> <tr> <td>6 – 12 months:</td> <td>2.5 ml</td> <td>3 – 4 times / day</td> </tr> <tr> <td>1 – 3 years:</td> <td>5 ml</td> <td>3 times / day</td> </tr> <tr> <td>4 – 6 years:</td> <td>7.5 ml</td> <td>3 times / day</td> </tr> <tr> <td>7 – 9 years:</td> <td>10 ml</td> <td>3 times / day</td> </tr> <tr> <td>10 – 12 years:</td> <td>15 ml</td> <td>3 times / day</td> </tr> </tbody> </table> <p>For post immunisation fever: One 2.5 ml dose. If necessary one further 2.5 ml dose 6 hours later. No more than two 2.5 ml doses in 24 hours. If the fever is not reduced, consult your doctor.</p>	Age	Dose	Frequency	3 – 6 months (+ over 5kg):	2.5 ml	3 times / day	6 – 12 months:	2.5 ml	3 – 4 times / day	1 – 3 years:	5 ml	3 times / day	4 – 6 years:	7.5 ml	3 times / day	7 – 9 years:	10 ml	3 times / day	10 – 12 years:	15 ml	3 times / day	<p align="center">  IBUPROFEN FOR CHILDREN 100mg/5ml ORAL SUSPENSION 100ml BOTTLE </p> <p align="center"> For children from 3 months Colour & Sugar Free 100ml e </p>	<p>WARNINGS Do not exceed the stated dose. For short term use only. Do not give to infants aged 3 - 6 months for more than 24 hours, or children over 6 months for more than 3 days. If symptoms persist for longer than these times, or worsen, consult your doctor. Do not let your child take this medicine if they are allergic to ibuprofen or any of the other ingredients, aspirin, or related painkillers, or have (or have ever had) a stomach ulcer, perforation or bleeding. Consult your doctor or pharmacist if your child suffers from asthma, is taking other pain relief or is on any regular treatment. Pregnant women should obtain medical advice before using. Do not use after the date shown on the pack. Please read enclosed leaflet before use. Keep all medicines out of the reach and sight of children.</p> <p>INGREDIENTS: Each 5ml spoonful of oral suspension contains: Active ingredients: ibuprofen 100mg. Also contains: Maltitol liquid. See leaflet for more information. (IN)</p> <p>MA holder: Wrafton Laboratories Ltd, PL 12063/0060. Exp ‘Paramed’ is a registered trademark. © Wrafton Laboratories Ltd, 2006.  </p>
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LABEL



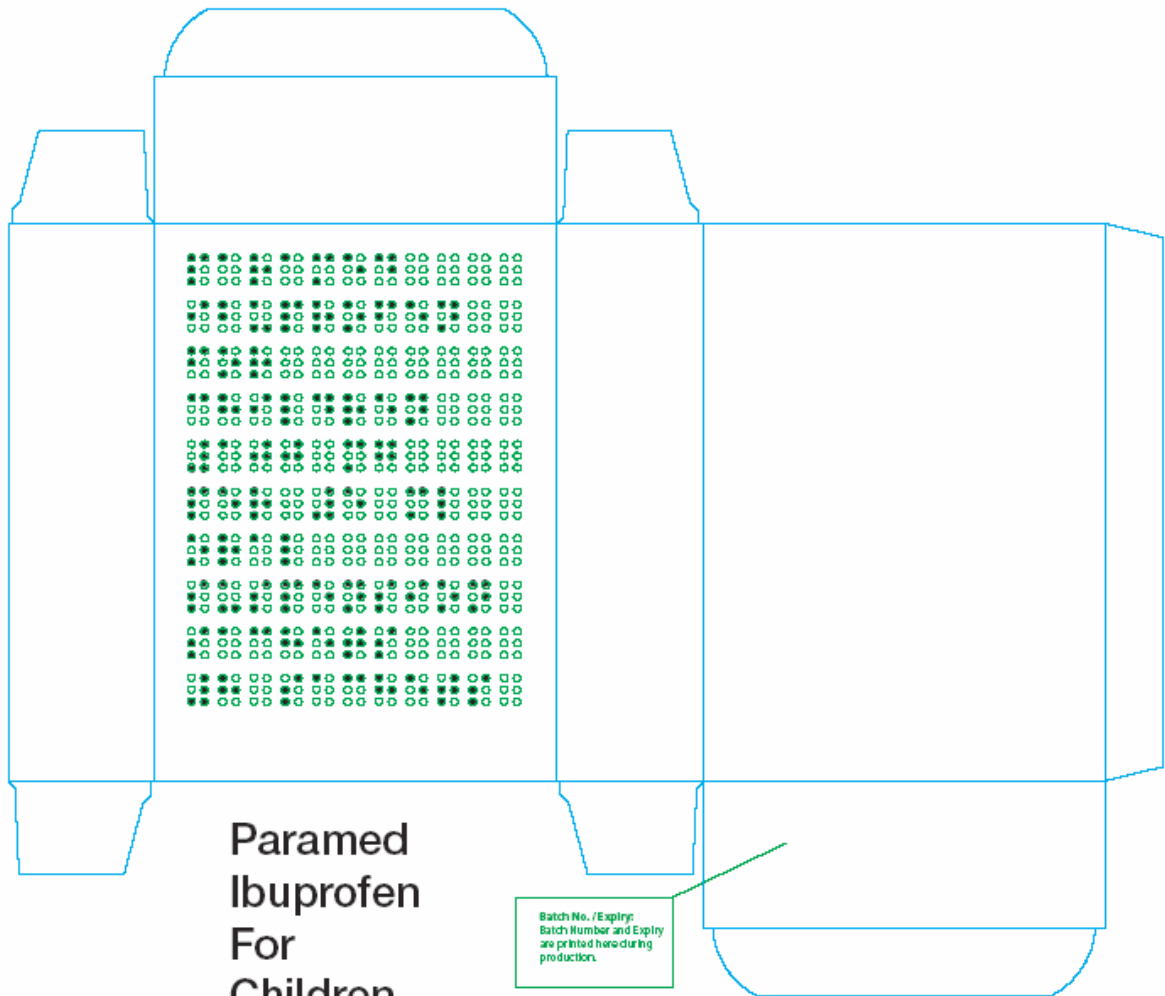
PARAMED IBUPROFEN FOR CHILDREN 100 MG/5 ML ORAL SUSPENSION
PL 12063/0060

LABEL



**PARAMED IBUPROFEN FOR CHILDREN 100 MG/5 ML ORAL SUSPENSION SACHETS
PL 12063/0061**

LABEL



**Paramed
Ibuprofen
For
Children
#ajj mg
per #e ml
oral
suspension
sachets
#h sachets**

Batch No. / Expiry:
Batch Number and Expiry
are printed here during
production.

PARAMED IBUPROFEN FOR CHILDREN 100 MG/5 ML ORAL SUSPENSION SACHETS
PL 12063/0061

LABEL

paramed
IBUPROFEN FOR CHILDREN
100mg/5ml ORAL SUSPENSION SACHETS
5ml SACHET

ORANGE FLAVOUR

Fast & effective relief from fever and pain

For children from 3 months
Colour & Sugar Free

Relieves fever, including post-immunisation fever. Relieves cold and flu symptoms and mild to moderate pain including sore throat, swelling pain, toothache, headache, minor cuts & sprains.

DIRECTIONS FOR USE
For oral use: Sprinkle sachet into little open and use measuring spoon for correct dose.

DOSEAGE
For children from 3 months: Not suitable for children under 3 months of age or weighing less than 5kg. Leave at least 4 hours between doses.
For Pain & Fever:

Age	Dose	Frequency
3 – 6 months (+ over 5kg)	2.5 ml	3 times / day
6 – 12 months:	2.5 ml	3 – 4 times / day
1 – 3 years:	5 ml	3 times / day
4 – 6 years:	7.5 ml	3 times / day
7 – 12 years:	10 ml	3 times / day

For Post-immunisation Fever:
One 2.5 ml dose. If necessary one further 2.5 ml dose 4 hours later. No more than two 2.5 ml doses in 24 hours. If the fever is not reduced, consult your doctor.

WARNINGS
Do not exceed the stated dose. For short-term use only. Do not give to infants aged 3 – 6 months for more than 24 hours, or children over 6 months for more than 3 days. If symptoms persist for longer than these times, or worsen, consult your doctor. Do not let your child take this medicine if they are allergic to ibuprofen or any of the other ingredients, aspirin, or related substances, or have (or have ever had) a stomach ulcer, peptic ulcer or bleeding. Consult your doctor or pharmacist if your child suffers from asthma, is taking other pain relief or is on any regular treatment. Pregnant women should consult medical advice before using. Do not use after the date shown on the pack. Please read and understand the leaflet before use. Do not store above 25°C. KEEP ALL MEDICINES OUT OF THE REACH AND SIGHT OF CHILDREN.

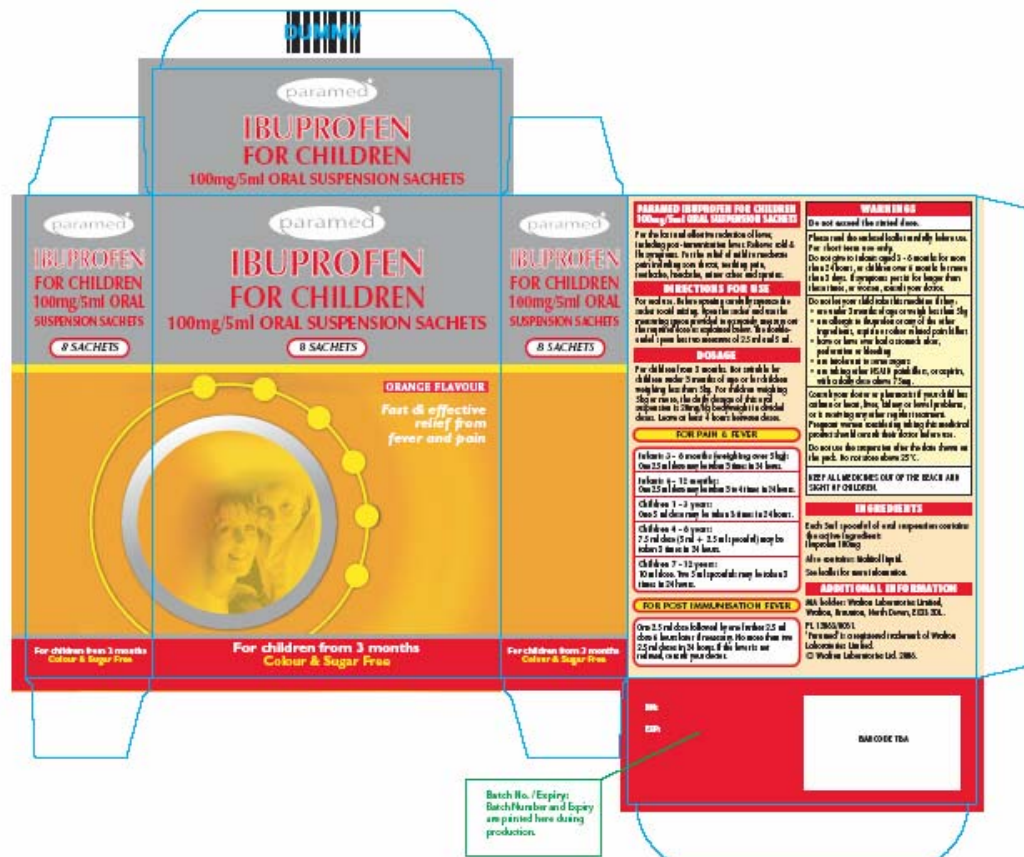
INGREDIENTS: Each 5ml sachet contains oral suspension contains:
Active ingredient: Ibuprofen 100mg.
Also contains: Methyl Hydroxy. See leaflet for more information.
MA holder: Winthrop Laboratories Limited, PL 12063/0061.
Paramed is a registered trademark.

BN Exp

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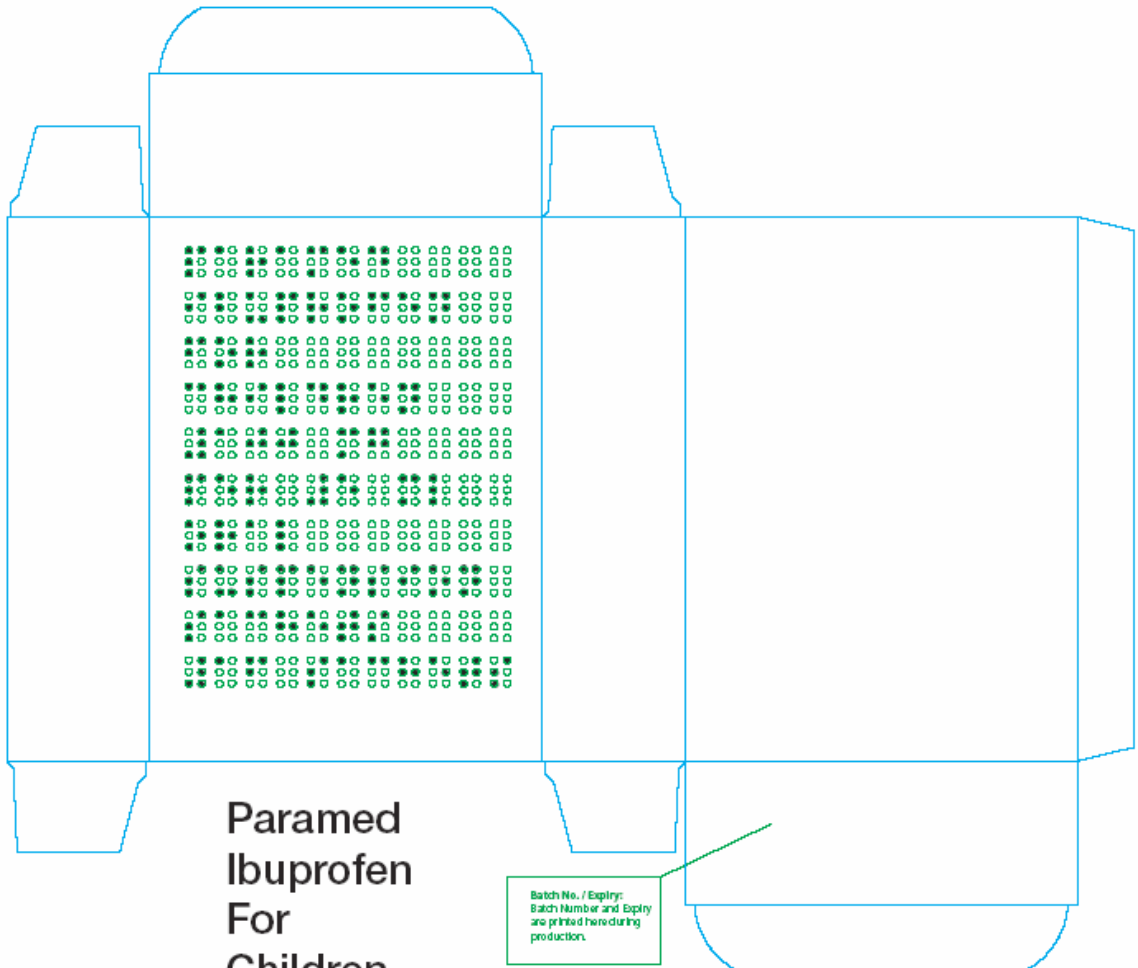
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PL 12063/0061

LABEL



**PARAMED IBUPROFEN FOR CHILDREN 100 MG/5 ML ORAL SUSPENSION SACHETS
PL 12063/0061**

LABEL



**Paramed
Ibuprofen
For
Children
#ajj mg
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