Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

Ibuprofen

DE/W/040/pdWS/001

Rapporteur:	Germany (DE)
Finalisation procedure (Day 120):	11.11.2013
Date of finalisation of PAR:	21.01.2014

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VII
INN (or common name) of the active substance(s):	Ibuprofen
MAH (s):	See section VII
Pharmaco-therapeutic group (ATC Code):	Anti-inflammatory and antirheumatic products, non-steroids; propionic acid derivative (ATC Code: M01AE01)
Pharmaceutical form(s) and strength(s):	See section VII

I. EXECUTIVE SUMMARY

SmPC changes are proposed for sections 4.2, 4.4 and the corresponding sections of the PL.

Summary of outcome

☒ Change

☒ **Paediatric information clarified: section 4.2, 4.4**

II. RECOMMENDATION

The purpose of Art 45 procedure is to update the knowledge about paediatric application, and to update the SmPC and PL if necessary. For ibuprofen only a few updates relating to the safety information and the treatment duration are considered indicated.

Recommendation
The appropriate variation to be requested from the MAH within 60 days to introduce the recommended wording (please refer to Section VI) for the paediatric population in the SmPCs and PLs.

III. INTRODUCTION

In accordance with Article 45 of the Regulation (EC) No. 1901/2006, studies assessed by the MAHs in this procedure are paediatric studies completed before 26 January 2007, which have not previously submitted.

This Article 45 Worksharing Procedure concerns ibuprofen. Ibuprofen is a propionic acid, non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic actions. It is a non-specific inhibitor of cyclo-oxygenase. It is a chiral compound and its pharmacological activity is mainly dependent on the S(+) enantiomer. It was developed in the 1950/60s and was initially marketed for prescription use for its anti-rheumatic activity, being introduced in the United Kingdom (UK) in 1966 and in the United States of America (USA) in 1974. A substantial body of information has since been developed to support use of ibuprofen as a non-prescription medicine for a range of specified indications. In 1983 it became the first NSAID to be approved for over-the-counter (OTC) use in the UK. In the following year it became available OTC in the USA. It is now available OTC in many markets worldwide, including the majority of EU Member States. However, the prescription status is varying between the EU Member States.

The age limit for children varies according to strength, formulation and indication.

Pharmaceutical formulations used in the submitted clinical studies concern almost solely the oral formulations. Only one study NL0113 (open label, non-comparative) listed by Reckitt Benckiser investigated ibuprofen 60/125 mg suppositories. No study data concerning the ibuprofen formulation 5/20% gel were provided. No study data regarding the intravenous ibuprofen formulation were submitted.

This assessment report concerns especially the oral formulations due to the MAHs' submitted data.

The submitted studies provide no new insights in the efficacy of ibuprofen in the symptomatic treatment of mild to moderate pain, and/or fever in children (≥ 5 kg body weight / from 6 months and above and from 3 months and above, respectively) and adolescents.

Reckitt Benckiser's submitted study data (M84162 Part 2, M88126, M86088, M83104, BPI301) are considered not sufficient to recommend ibuprofen for the symptomatic treatment of pain and inflammation in rheumatic diseases within the scope of this procedure.

The actual state is that between different EU Member States the indication wording varies to some extent: See pp. 22 – 55, Appendix 1, clinical overview of Johnson & Johnson, see pp. 22 -

30, section 6.1, clinical overview of Pfizer and see Appendix 3 of Reckitt Benckiser's response document.

The dose recommendation for ibuprofen in the symptomatic treatment of mild to moderate pain, and/or fever in children and adolescents depends on body weight and age respectively – in general with 7 to 10 mg/kg body weight as single dosage, up to a maximum of 30 mg/kg body weight as total daily dosage.

Two MAHs (Johnson & Johnson and Pfizer) submitted numerous paediatric studies for ibuprofen, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.
The Rapporteur received the submission of Reckitt Benckiser after finalisation of the day 89 draft AR during the clock-stop phase - assessment is included in section VI.2 below.

Short critical expert overviews have also been provided.

The MAH Johnson & Johnson stated that the submitted paediatric studies do not influence the benefit risk for ibuprofen and that there is no consequential regulatory action. Also Reckitt Benckiser remarked that many of the studies are old, and not reported to current standards.

In addition, the following documentation has been included as per the procedural guidance:

For Johnson & Johnson and Reckitt Benckiser:

- A line listing

- An annex including SPC wording of sections 4.1 and 4.2 related to the paediatric use of the medicinal products.

For Pfizer:

- A line listing

- An annex including the indication wording related to the paediatric use of the medicinal products.

- The relevant SPCs were reviewed for paediatric dosing regimens. Most of the SPCs reviewed contain dosing for adults and children over 12 years of age. The dosing for this age group was within the range of 200-400 mg in divided doses up to a maximum daily dose of 1200mg. Some of the SPCs contained dosing for children ages 6-12 years. These dosing regimens are also within the dosing regimens provided in the Ibuprofen CDS.

- Referring to paediatric dosing (by age/weight range) for children ages 2-12 years and dosing (by age) for adults and children over 12 years. Since the kg weight for children of age 12 is specified as 43 kg, then the weight relative to the age group of 12 years and older would be >43 kg.

- Since the SPC dosing regimens are consistent with the Ibuprofen CDS dosing, the reference label for this report is the current effective Ibuprofen CDS, Version 12.0 effective 06-Apr-2011, instead of each of the individual SPCs.

- A table has been included on the next page showing the recommended dosing as specified for children ages 2 to 12 years old, and the dosing for age 12 years and over, which covers the paediatric age range of 12-18 years.

Age	**Weight**	**Dose**	**Maximum Daily Dose**
2-3 years	24-35 lbs or 11-15 kg	100 mg up to 4 times a day	400 mg
4-5 years	36-47 lbs or 16-21 kg	150 mg up to 4 times a day	600 mg
6-8 years	48-59 lbs or 22-26 kg	200 mg up to 4 times a day	800 mg
9-10 years	60-71 lbs or 27-32 kg	250 mg up to 4 times a day	1000 mg
11-12 years	72-95 lbs or 33-43 kg	300 mg up to 4 times a day	1200 mg

12+ years	> 43 kg	Up to 400 mg up to 3 times daily	1200 mg

Assessor's comment:
In this table the maximum daily dose is considered too high except the last category (12+ years; > 43 kg). The normally recommended maximum daily dose for the 'symptomatic treatment of mild to moderate pain and/or fever' in children and adolescents is 30 mg ibuprofen/kg body weight.
In accordance with recently finalized DC procedures (DE/H/3341/001-002/DC; DE/H/2597-2598/001-002/DC) the Rapporteur recommends that the kg body weight for children of age 12 is specified by 40 kg, then the weight relative to the age group of 12 years and older would be ≥40 kg.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical studies

Ibuprofen is available in oral (tablets, capsules, effervescent tablets, granules, powder, suspension) rectal, topical and parenteral formulations.

Pharmaceutical formulations used in the clinical studies almost entirely concern the oral formulations.
However, in the subsequent section V. Assessment of Response to Questions and Assessment of Reckitt Benckiser's Submission, p. 67, also one study NL0113 (open label, non-comparative) is stated investigating ibuprofen 60/125 mg suppositories in juvenile pyrexia.

IV.2 Non-clinical aspects

Not applicable.

IV.3 Clinical aspects

1. Introduction

Pharmaceutical formulations used in the submitted clinical studies listed in this section IV concern only oral formulations.
The submitted studies provide no new insights in the efficacy of ibuprofen in the symptomatic treatment of mild to moderate pain, and/or fever in children and adolescents.
The submitted study data listed in this section IV do not concern children younger than 6 months. Further, concerning the submission of Johnson & Johnson and Pfizer no study data were submitted with regard to pain and inflammation in rheumatic disease including juvenile idiopathic arthritis.
The actual state is that between different EU Member States the indication wording varies to some extent: See pp. 22 – 55, Appendix 1, clinical overview of Johnson & Johnson and pp. 22 - 30, section 6.1, clinical overview of Pfizer.

The submission of Johnson & Johnson contains:

22 clinical trials examining the use of ibuprofen as a mono product (20) or as combination product (2) in studies with children were retrieved and are tabulated in the next subsection in tabular format under “2. Clinical Studies”.

38 clinical trials examining the use of ibuprofen in a mixed population (mainly persons > 18 years with few adolescents between 15 and 18 years) were retrieved and are tabulated in the next subsection in tabular format under “2. Clinical Studies”. But not further evaluated due to impossibility to separate out those under 18 years in these reports, and given the mean age is relatively high there is nothing specific to say regarding younger patients. The studies are in general terms both compatible in dose and observed efficacy.

Study reports were evaluated for consistency with clinical particulars and pharmacological profiles detailed in SmPCs, and where this was not apparent, further analysis was performed to assess study quality, relevance and potential impact of discrepancies.

The reports numbers in the naming of the files and the report numbers/study identifiers in the following text are not identical! The protocol numbers are added for verification.

Overview of Pharmacokinetics:
MCPC Statistical Report No. 106 of Protocol 86-642: A RANDOMIZED, OPEN LABEL, PARALLEL, SINGLE DOSE STUDY OF THE ANTIPYRETIC EFFICACY, SAFETY, AND BLOOD LEVELS OF IBUPROFEN 6 MG/KG IN FEBRILE CHILDREN WITH ACETAMINOPHEN 10-15 MG/KG AS A POSITIVE CONTROL FOR EFFICACY.
Activity was evaluated using temperature reduction as indicator. Efficacy and safety are discussed in subsequent sections.
Serum ibuprofen levels were in expected range (around 28 µg/ml) for 6mg / kg bodyweight. Tmax was also in the expected range (around 1 hour) for a suspension. The lag time between Cmax and maximum temperature was around 3 hours (as expected).
MCPC Statistical Report No. CPR-149 of Protocol 97-024: MULTIPLE-DOSE PHARMACOKINETIC STUDY OF AN IBUPROFENPSEUDOEPHEDRINE HCI SUSPENSION IN CHILDREN.
Twenty-four healthy children ages 4 through 11 years were enrolled in the study. Each dose provided 7.5 mg/kg of ibuprofen. AUCt; $C_{AVG,SS}$; $C_{MAX,SS}$; $C_{MIN,SS}$; $T_{MAX,ss}$; Cl/F; Vd/F; kA; kEL; t½; and FI were determined. All values were in the expected range for a suspension dose 7,5mg/kg BW.
Pharmacokinetic profiles confirmed that ibuprofen did not accumulate in children with multiple-dosing.

Assessor’s comment:
In the multiple-dose pharmacokinetic study (Protocol 97-024) ibuprofen and pseudoephedrine were administered concurrently. However, this combination cannot be considered representative for ibuprofen as a single agent.
According to the MAH the PK studies provide no new insights in the kinetics of ibuprofen.

Overview of Efficacy:
Efficacy data are considered by the primary study objective – pain relief or temperature reduction (fever) or non labelled indications. The trials in paediatric populations cover age

groups in pain studies 5 years to 11 years and in fever studies 6 month to 11 years.
A separation in <2 years, 2 to 5years and 6 to 11 years is not possible.

Pain

MCPC Statistical Report No. 161 of Protocols 90-002 &90-003: A COMPARISON OF THE EFFICACY AND SAFETY OF IBUPROFEN SUSPENSION DOSED AT 5 MG/KG AND 10 MG/KG AND ACETAMINOPHEN ELIXIR DOSED AT 12.5 MG/KG TO PLACEBO IN CHILDREN WITH EAR PAIN.
158 children ages 4 through 13 years (75 with ibuprofen [age 5 – 13] were enrolled in the study.
Indication was acute ear pain due to acute otitis media. Ibuprofen 10 mg/kg was significantly better than placebo from 2-3 hours post-dose to 6 hours; ibuprofen 5 mg/kg was significantly better than placebo from 3-4 hours post-dose to 6 hours; differences between ibuprofen 5 mg/kg and ibuprofen 10 mg/kg were not significantly different although a trend for 10 mg/kg is seen (PID).

MCPC Statistical Report No. 162 of Protocols 89-949 &90-001: A COMPARISON OF THE EFFICACY AND SAFETY OF IBUPROFEN SUSPENSION DOSED AT 5 MG/KG AND 10 MG/KG AND ACETAMINOPHEN ELIXIR DOSED AT 12.5 MG/KG TO PLACEBO IN CHILDREN WITH SORE THROAT PAIN.
260 children ages 5 through 12 years (133 with ibuprofen [age 5 – 12] were enrolled in the study.
IBU at 5mg/kg and 10mg/kg was significantly or marginally significantly better than placebo from 1-2 hours post-dose to 6 hours on all but the verbal scale (PID).
Analysis of the Global Assessments of treatment efficacy indicated that there was a significant Age by Treatment interaction for this parameter. Pairwise comparisons of the treatments within age categories showed that IBU at both 5mg/kg and 10mg/kg were statistically superior to placebo in both age groups.
Separate analysis of the age groups 5-7 years and 8-12 years did not show significant differences.

MCPC Statistical Report No. 187 of Protocol 90-048: A SINGLE DOSE STUDY TO COMPARE THE EFFICACY AND SIDE EFFECTS OF IBUPROFEN SUSPENSION TO PLACEBO IN CHILDREN 5 THROUGH 11 YEARS OF AGE WITH POST-OPERATIVE PAIN SECONDARY TO EITHER INGUINAL OR UMBILICAL HERNIORRHAPHY.
45 children ages 5 through 11 years (30 with ibuprofen [age 5 – 11] were enrolled in the study.
The study was discontinued due to low/slow enrolment. No efficacy data are reported

Assessor's comment:
The MAH stated that the abovementioned studies provide no new insights in the efficacy of ibuprofen in pain treatment of children and adolescents.
The above described studies revealed no special new aspects regarding the generally accepted indication wording 'symptomatic treatment of mild to moderate pain' for ibuprofen in children and adolescents.
In the two abovementioned pain studies (Protocols 90-002 &90-003; Protocols 89-949 &90-001) conclusions were not provided in the clinical study report. Further, only single dose treatment was studied which has insufficient informative value. A multiple dose study would be more meaningful. As well as the study design is not fully conform with OTC use (treatment duration up to 3 or 4 days; maximum daily dose of 30 mg ibuprofen/kg).

Temperature reduction (fever)
MCPC Statistical Report No. 80 of Protocol 5-535: A SINGLE DOSE DOUBLE-BLIND STUDY COMPARING THE EFFICACY OF IBUPROFEN AND CHILDREN'S TYLENOL ELIXIR.
50 children (49 evaluated) were enrolled in the study. Average age for 23 ibuprofen patients was 2.3 years. Dosing for paracetamol was 10 – 15 mg/ kg, dosing of Ibuprofen was 6-7mg/kg. There was no significant difference between the efficacy parameters of both groups:
There was no significant difference between drugs with respect to the sum of the temperature differences from baseline (SUMDIFF) or MAXDIFF. A repeated measures analysis of variance on the temperatures showed no significant differences between drugs. There was no significant difference between drugs with respect to the number of hours a patient's condition was rated as "improved" compared to baseline.
No further conclusions from this study.

MCPC Statistical Report No. 84 of Protocol 6-639: A COMPARATIVE DOSE RANGE EVALUATION OF THE ANTIPYRETIC EFFICACY AND SAFETY OF IBUPROFEN LIQUID AT THREE DIFFERENT DOSES IN CHILDREN.
129 children (126 evaluated) (94 with ibuprofen [age 8m– 6y]) were enrolled in the study.
3 mg/kg, 6 mg/kg, and 9 mg/kg ibuprofen were compared with 12 mg/ kg paracetamol. Analysis of the main effects of drugs showed that paracetamol 12 mg/kg and ibuprofen 3 mg/kg were the same and together resulted in significantly lower responses than ibuprofen 9 mg/kg while ibuprofen 6 mg/kg was equivalent to ibuprofen 9 mg/kg on all measures (TEMPDIFF, SUMDIFF, MAXDIFF). Ibuprofen 6 mg/kg was found to be statistically equivalent to paracetamol 12 mg/kg on SUMDIFF, significantly superior to paracetamol 12 mg/kg on MAXDIFF, and nearly significantly superior to paracetamol 12 mg/kg on TEMPDIFF. In addition, all three measures exhibited a significant linear association with ibuprofen dosage indicating that increasing doses of ibuprofen resulted in a greater response.
No further conclusions from this study.

MCPC Statistical Report No. 85 of Protocol 6-640: A MULTIPLE DOSE STUDY COMPARING THE ANTIPYRETIC EFFICACY AND SAFETY OF 5 - 7 MG/KG OF IBUPROFEN LIQUID AND 10 - 15 MG/KG OF ACETAMINOPHEN LIQUID IN FEBRILE CHILDREN.
413 children (386 evaluated) were enrolled in the study.
363 children ages 6 month through 11 years (274 with ibuprofen [age 6m – 11y]) were finally evaluated.
Temperatures were recorded at -¼, 0, 2, 4, 6, and 8 hours and at least once every 8 hours for up to four days. Treatments were administered q4h prn up to 4 d; max 4 doses/d Ibuprofen was superior to paracetamol with respect to SUMDIFF and MAXDIFF. There were no significant differences between drugs with respect to the number of doses given on each day or the total number of doses given over all four days. Ibuprofen was given a significantly higher global rating than acetaminophen on days 1 and 2. There were no significant differences the other two days.

MCPC Statistical Report No. 136 of Protocol 88-828: A DOSE RANGE STUDY OF THE ANTIPYRETIC EFFICACY AND SAFETY OF IBUPROFEN PEDIATRIC SUSPENSION IN FEBRILE CHILDREN.
36 children ages were enrolled in the study instead of 160 planned patients.
The study was discontinued due to low/slow enrolment. No efficacy data are reported

MCPC Statistical Report No. 149 of Protocol 89-932: A SINGLE DOSE STUDY TO COMPARE THE EFFICACY OF ACETAMINOPHEN ELIXIR DOSED AT 12.5 MG/KG AND 25 MG/KG AND IBUPROFEN SUSPENSION DOSED AT 5 MG/KG AN'D 10 MG/KG IN FEBRILE CHILDREN.

Two hundred eighty four (284) patients were entered into the study with 275 eligible for the efficacy analysis (137 with ibuprofen [age 2y– 11y]).
Temperatures were measured at baseline, and hourly for eight hours.
APAP 25 mg/kg and ibuprofen 10 mg/kg were superior to APAP 12.5 mg/kg and ibuprofen 5 mg/kg in both the low and high fever groups; however, there were no significant differences between ibuprofen 5 mg/kg and APAP 25 mg/kg in the high fever group.
The maximum reduction of temperature was 2°C (3.5°F) after 3 hours.

MCPC Statistical Report No. 155 of Protocol 89-945: A SINGLE DOSE STUDY TO COMPARE THE EFFICACY OF ACETAMINOPHEN ELIXIR DOSED AT 10-15 MG/KG AND IBUPROFEN SUSPENSION DOSED AT 5 MG/KG AND 10 MG/KG IN FEBRILE CHILDREN.
A total of 273 patients were entered into the study with 259 eligible for analysis (178 with ibuprofen [age 2y – 11y]).
Patients were pre-stratified on the basis of their baseline temperature ('low' or 'high').
For the combined fever group, Ibu 10 mg/kg was significantly better than APAP 10-15 mg/kg at hours 3 through 7 and for all four summary measures, and significantly better than Ibu 5 mg/kg at hour 5 and for SUMDIFF - 6 hours. For the low initial fever group, Ibu 10 mg/kg was significantly better than APAP 10-15 mg/kg at hours 3 and 6 and for SUMDIFF over 4 and 6 hours and for MAXDIFF. For the high initial fever group, Ibu 10 mg/kg was significantly better than APAP 10-15 mg/kg at hours 4, 5 and 7 and for all four summary measures. Ibu 5 mg/kg was not significantly different from APAP 10-15 mg/kg for any measure. Parents rated Ibu 10 mg/kg superior to APAP 10-15 mg/kg in both effectiveness and acceptability for all fever groups. Ibu 5 mg/kg had higher ratings than APAP 10-15 mg/kg in acceptability for the combined fever groups. Also, Ibu 10 mg/kg was superior to Ibu 5 mg/kg in effectiveness for the low fever group and in acceptability for the combined fever group. The maximum reduction of temperature was1.8°C (3.2°F) after 4 hours.

MCPC Statistical Report No. 167s of Protocol 91-113: EFFICACY AND PHARMACOKIN"ETIC/PHARMACODYNAMIC PROFILE OF IBUPROFEN CHEWABLE TABLETS VERSUS IBUPROFEN SUSPENSION IN FEBRILE CHILDREN.
A total of 85 patients were entered into the study with 71 children ages 2 through 11 years eligible for efficacy analysis.
The treatments were compared in a randomized, open-label, parallel, single-dose study.
Prior to randomization to either the tablet or suspension treatment, patients were pre-stratified on the basis of their baseline temperature into either a low fever group (101.0°F- 102.5°F orally) or a high fever group (> 102.5 °F - 104.5 °F orally). Patients in the low fever group received ibuprofen at 5 mg/kg; patients in the high fever group received ibuprofen at 10 mg/kg.
Temperatures were recorded at 15, 30, 45, 60, and 90 minutes and at 2, 3, 4, 5, 6, 7, and 8 hours·(and at 9 or 10 hours if a blood sample was collected at that time). The following endpoints were analyzed:

- Temperature differences from baseline at each measurement interval
- Area under the temperature reduction versus time curves and the maximum temperature reduction over 8 hours
- Number of hours a temperature reduction of at least 1 °F was achieved

Clinical Response: In almost all of the tested parameter there were no statistically significant differences between tablets and suspension – the observed statistical significant differences are not clinically relevant.

MCPC Clinical Study Report No. 190 of Protocol 91-140: A SINGLE DOSE STUDY TO COMPARE THE EFFICACY OF ACETAMINOPHEN SUSTAINED RELEASE PEDIATRIC CHEWABLE TABLETS TO IBUPROFEN SUSPENSION IN FEBRILE CHILDREN

A total of 218 patients (145 with ibuprofen [average age 5.4y]) were entered into this study
This was a randomized, single-dose, double-blind, parallel study comparing sustained release pediatric acetaminophen chewable tablets dosed at 20 to 30 mg/kg and a ibuprofen suspension dosed at 5 mg/kg and 10 mg/kg in the treatment of ambulatory febrile children. Qualified subjects were stratified into two groups: High Fever (>102.5°F) or Low Fever (<102.5°F). Temperatures and clinical evaluations were recorded at 1, 2, 3, 4, 5, 6, 7, and 8 hours after drug administration.
The results of analysis of variance indicated that there were no significant differences between acetaminophen sustained release chewable tablets and the two doses of ibuprofen suspension with respect to areas under the temperature reduction time curve (SUMDIFF) and the maximum temperature reduction over eight hours (MAXDIFF). Inspection of the temperature reduction curve shows that all three treatments have a comparable onset of antipyretic activity.
There were no significant differences among APAP SR chewable tablets, IBU 10 mg/kg suspension and IBU 5 mg/kg suspension with regard to the number of hours a temperature reduction of a least one degree was achieved, the assessment of effectiveness and the overall acceptability of treatments.

MCPC Clinical Study Report No. 206 of Protocol 93-330: A PHASE III SINGLE DOSE STUDY TO COMPARE THE EFFICACY OF IBUPROFEN CHEWABLE TABLETS TO IBUPROFEN SUSPENSION IN FEBRILE CHILDREN.
This was a randomized, parallel, single dose, double-blind, multi-center study using double dummy design. Patients were stratified into the low (5 mg/kg) or high (10 mg/kg) dose group depending on their baseline temperature: High Fever (>102.5°F) or Low Fever (<102.5°F). The antipyretic efficacy was evaluated for eight hours following a single dose.
Two hundred twenty-seven (227) patients [age 2y – 11y] were enrolled in this study of which two hundred twenty-two (222) had efficacy data. Two hundred thirteen (213) were eligible for the per protocol analyses. One hundred eleven (111) patients were entered into the high dose group (53 taking tablets, 58 taking suspension) and 116 patients were entered into the low dose group (58 taking tablets, 58 taking suspension).
All children received a single dose of both chewable tablets and liquid suspension, one or the other preparation was placebo. Temperature was measured at 30 minutes and at 1, 2, 3, 4, 5, 6, 7, and 8 hours after dosage. Clinical response was assessed at the same time as temperature.
In the low dose group, tablets and suspension were equally effective for all efficacy criteria. In the high dose group the ibuprofen tablets provided significantly more hours of improvement of clinical response than ibuprofen suspension, and there was a greater temperature reduction at hours four and five for the tablets which reached statistical significance in the per protocol analyses; however, both suspension and tablets were clinically comparable and effective throughout eight hours.

MCPC Clinical Study Report No. 214 of Protocol 94-437: A SINGLE DOSE, RANDOMIZED, INVESTIGATOR-BLINDED TRIAL TO COMPARE THE EFFICACY AND SAFETY OF IBUPROFEN SUSPENSION 7.5 MG/KG WITH ACETAMINOPHEN SUSPENSION 12.5 MG/KG FOR THE TREATMENT OF FEBRILE CHILDREN.
A total of 111 patients (55 with ibuprofen [age 2y– 11y]) were entered into this study with 108 patients eligible for the intent-to-treat analysis and 87 patients eligible for the per-protocol analysis.
Temperatures were measured at hours .25, .50, 1, 2, 3, 4, 5, 6, 7 and 8 hours after the administration of study medication.
Patients taking ibuprofen 7.5 mg/kg had significantly greater percent temperature reduction than patients taking APAP 12.5 mg/kg from hours 1 to 7 in the combined fever group.
Ibuprofen 7.5 mg/kg was significantly better than APAP 12.5 mg/kg in sum of temperature differences from baseline (SUMDIFF) over 4, 6 and 8 hours for the combined fever group and the high fever group.

A single dose of ibuprofen 7.5 mg/kg suspension provides significantly greater overall temperature reduction over eight hours compared to a single dose of acetaminophen 12.5 mg/kg suspension. Ibuprofen 7.5 mg/kg maintains a mean temperature reduction of at least 1°F for nearly eight hours. Acetaminophen 12.5 mg/kg maintains a mean temperature reduction of at least 1°F for four hours.
The maximum reduction of temperature for both products was after 3 hours.

MCPC Clinical Study Report No. 226 of Protocol 95-516: A SINGLE-DOSE, RANDOMIZED, INVESTIGATOR-BLINDED TRIAL TO COMPARE THE EFFICACY AND SAFETY OF IBUPROFEN SUSPENSION 7.5 MG/KG WITH ACETAMINOPHEN SUSPENSION 12.5 MG/KG FOR THE TREATMENT OF FEBRILE PATIENTS.
A total of 74 patients (35 with ibuprofen [age 1y– 11y])were entered into the study with 73 eligible for all intent-to treat analyses and 55 eligible for all per-protocol analyses.
Qualified subjects were stratified into two groups: High Fever (>102.5°F) or Low Fever (<102.5°F). Following the recording of baseline temperature and the administration of study medication, temperature readings were taken relative to baseline at 15, 30, 45 and 60 minutes and 2, 3, 4, 5, 6, 7 and 8 hours.
Single doses of ibuprofen 7.5 mg/kg and acetaminophen 12.5 mg/kg suspensions were clinically equally effective in temperature reduction, based on the weighted sums of temperature differences and the weighted sums of percent temperature differences, during the first four hours after administration in patients with fever. A single dose of ibuprofen 7.5 mg/kg suspension was not significantly different in duration of effect, using the protocol definition of time until rescue, than paracetamol 12.5 mg/kg suspension; however, ibuprofen maintained a significantly greater temperature reduction from hours 4-8.
The maximum reduction of temperature for both products was after 3 hours.

MCPC Clinical Study Report No. 256 of Protocol 96-608: A SINGLE-DOSE, RANDOMIZED, DOUBLE-BLIND TRIAL TO COMPARE THE EFFICACY AND SAFETY OF IBUPROFEN SUSPENSION 7.5 MG/KG WITH ACETAMINOPHEN SUSPENSION 12.5 MG/KG FOR THE TREATMENT OF FEBRILE CHILDREN.
110 subjects (55 with ibuprofen [age 2y– 11y]) were enrolled in the study. Qualified subjects were stratified into two groups: High Fever (>102.5°F) or Low Fever (<102.5°F). Following the recording of baseline temperature and the administration of study medication, temperature readings were taken relative to baseline at .25, .50, 1, 2, 3, 4, 5, 6, 7 and 8 hours.
For the primary endpoint of temperature differences from baseline at each measurement interval, the response profiles for ibuprofen and paracetamol were similar. Subjects treated with ibuprofen exhibited significantly greater temperature reduction at hours four and five. Similar results were observed for both the intent-to-treat and the per-protocol analysis. For the secondary endpoint of weighted sum of temperature differences from baseline, subjects treated with ibuprofen exhibited greater temperature reduction than paracetamol over the four, six and eight hour intervals for both the intent-to-treat and per-protocol analysis. The response profiles for both ibuprofen and paracetamol were similar for percent temperature reduction at each measurement interval.
The maximum reduction of temperature for both products was after 3 hours, 1,7°C (3,0°F) for ibuprofen and 1,4°C (3,0°F) for paracetamol.

MCPC Clinical Study Report No. 257 of Protocol 96-619: A PHASE IV, RANDOMIZED, DOUBLE-BLIND, MULTICENTER TRIAL TO COMPARE THE SAFETY AND EFFICACY OF ACETAMINOPHEN SUSPENSION AND IBUPROFEN SUSPENSION IN THE TREATMENT OF FEBRILE CHILDREN.
280 subjects [age 2y – 11y] were enrolled in the study. There were 278 subjects included in the intent-to-treat efficacy analysis and 243 subjects in the per protocol efficacy analysis.

Subjects on paracetamol received one dose of paracetamol at hour 0 and one dose of paracetamol at hour 4. Subjects on ibuprofen received one dose of ibuprofen at hour 0 and one dose of placebo at hour 4. Subjects were followed for 8 hours after the first dose.
The primary efficacy measures were weighted sum of temperature differences from baseline (SUMDIFF) over the intervals of 0 to 8 and 0 to 6 hours, and weighted sum of percent fever reduction (SUMPCT) over 8 and 6 hours.
There was no significant difference between ibuprofen 7.5 mg/kg given at hour 0 and paracetamol12.5 mg/kg given at hour 0 and 4 in total fever reduction over 8 hours. Ibuprofen 7.5 mg/kg given at hour zero provided significantly greater total fever reduction over 6 hours than paracetamol12.5 mg/kg given at hours 0 and 4.
The maximum reduction of temperature for both products was after 4 hours.

Assessor's comment:
According to the MAH these studies provide no new insights in the efficacy of ibuprofen in fever treatment of children and adolescents.
The indication 'symptomatic treatment of fever' is an approved indication of ibuprofen in children (≥ 5 kg body weight) and adolescents.
The usual recommended dosage of ibuprofen in children and adolescents depends on body weight and age respectively – in general with 7 to 10 mg/kg body weight as single dosage, up to a maximum of 30 mg/kg body weight as total daily dosage.
In the submitted studies more than 1300 paediatric patients aged 6 months to 11 years were treated with ibuprofen in fever. Efficacy of ibuprofen in the treatment of fever in the usual recommended dosage was confirmed.
Changes are not necessary.

Non labelled indications
MCPC Clinical Study Report No. CSR – 272 of Protocol 00-131: A COMPARATIVE STUDY OF COADMINISTERED DOSES OF IBUPROFEN AND PSEUDOEPHEDRINE HCI AND EACH DRUG ALONE IN THE TREATMENT OF PRIMARY NOCTURNAL ENURESIS IN CHILDREN.

This was a double-blind, double-dummy, placebo-controlled, randomized, parallel-group study. 318 subjects [age 6y – 11y] were enrolled in the study, 307 subjects completed.
Combined treatment with ibuprofen (12.5 mg/kg) and pseudoephedrine (15 mg or 30 mg) was significantly superior to placebo and pseudoephedrine alone, but was not significantly superior to ibuprofen alone, in the treatment of nocturnal enuresis as determined by the primary study endpoint of mean change from baseline in the number of wet nights during the 14-day treatment period. In addition, while ibuprofen alone was significantly superior to placebo, pseudoephedrine alone was not.

No conclusions can be drawn from this study on the efficacy of ibuprofen in the labelled indications.

Assessor's comment:
Primary nocturnal enuresis is a non-approved indication for ibuprofen. This study provides no new insights in the efficacy of ibuprofen in the symptomatic treatment of mild to moderate pain and/or fever in children and adolescents.

Overview of Safety
MCPC Clinical Study Report No. CSR – 239 R1 of Protocol 99-086: AN OPEN-LABEL STUDY OF THE SAFETY OF AN IBUPROFEN-PSEUDOEPHEDRINE HCL SUSPENSION IN CHILDREN.

114 subjects [age 2y – 11y] were enrolled in the study.
Overall, 18.4% of subjects reported adverse events and most were of mild to moderate intensity.
The most commonly reported adverse event was somnolence, reported in 7.0% of subjects. · No serious adverse events or deaths were reported.
No conclusions can be drawn on safety/tolerability of ibuprofen as a single agent from this study.

Assessor's comment:
The safety study (Protocol 99-086) investigates an ibuprofen-pseudoephedrine combination. So the contribution of each single agent might not be clear.

MCPC Clinical Study Report No. CSR – 231 of Protocol 90-056: AN ASSESSMENT OF THE SAFETY OF PEDIATRIC IBUPROFEN ("BOSTON UNIVERSITY FEVER STUDY").
This study was erroneous listed as unsubmitted but actually was submitted in the published version (Lesko SM, Mitchell AA: An assessment of the safety of pediatric ibuprofen: a practitioner-based randomized clinical trial. JAMA. 1995; 273:929-933) as part of the switch documentation in Germany and part of the clinical documentation of the MRP suspension.

Assessor's comment:
The study design called for 75,000 febrile children between the ages of 6 months and 12 years to be randomly assigned to treatment with acetaminophen suspension, at a dose of 12 mg/kg; ibuprofen suspension, at a dose of 5 mg/kg; or ibuprofen suspension, at a dose of 10 mg/kg. The observed risk for acute gastrointestinal bleeding related to ibuprofen treatment was 4 per 55,785 children. While the observed risk for acute renal failure, anaphylaxis, and Reye Syndrome were 0 per 55,785. Please also refer to table 'Risk of Hospitalization with Selected Discharge Diagnosis Judged as Possibly Drug Related According to Antipyretic Assignment' below.

MCPC Clinical Study Report No. CSR – 231(S!) of Protocol 90-056: THE SAFETY OF ANTIPYRETIC MEDICATION USE AMONG CHILDREN LESS THAN TWO YEARS OF AGE: A SUBGROUP ANALYSIS OF THE BOSTON UNIVERSITY FEVER STUDY DATA.
This study was erroneous listed as unpublished but actually was submitted in the published version (Lesko SM, Mitchell AA: The Safety of Acetaminophen and Ibuprofen Among Children Younger Than Two Years Old. PEDIATRICS Vol. 104 No. 4 October 1999, http://www.pediatrics.org/cgi/content/full/104/4/e39) as part of the switch documentation in Germany and part of the clinical documentation of the MRP suspension.

As the BOSTON UNIVERSITY FEVER STUDY was the by far biggest safety study (with 55785 randomized to ibuprofen and more than 53000 treated) ever performed with ibuprofen in children.
It serves as the single reference for the safety review.
In this study the safety review was performed on those children who needed admission to the hospital.

Characteristics	Treatment Group		
	Acetaminophen (n=28 130)	Ibuprofen, 5 mg/kg (n=27 948)	Ibuprofen, 10 mg/kg (n=27 837)
Median age, mo (5th-95th percentile)	40 (8-117)	39 (8-118)	40 (8-118)
Median weight, kg (5th-95th percentile)	15 (8-35)	15 (8-34)	15 (8-34)
Male, %	52	52	51
Race, %			
White	66	66	66
African American	5.9	5.9	5.9
Latino	5.4	5.5	5.6
Asian	1.2	1.2	1.2
Other	2.3	2.4	2.3
Unknown	20	19	19

Table: Demographics of the 'BOSTON UNIVERSITY FEVER STUDY'

Treatment Group	**Acetaminophen 12 mg/kg n=28130**	**Ibuprofen (5mg/kg) n=27948_**	**Ibuprofen (10mg/kg) n=27837**
No. of Doses	%	%	%
1	5.8	5.0	5.2
2	8.1	7.1	7.1
3	9.0	8.8	8.6
4	9.8	9.3	9.4
5	7.5	7.1	7.7
6-10	27	28	27
11-15	11	12	12
16-20	4.4	5.1	5.2
>20	3.3	3.5	3.5
Unknown	8.8	9.1	9.1
None	4.6	4.5	4.4

Table: Cumulative Number of Doses of Study Medication Received According to Treatment Group

A total of 795 participants (1%) were admitted to a hospital in the 4 weeks following enrollment; for children in the acetaminophen, 5 mg/kg of ibuprofen, and 10 mg/kg of ibuprofen groups, the rates were 1%, 0.9%, and 1%, respectively.

Treatment Group	**Acetaminophen 12 mg/kg n=28130**	**Ibuprofen (5mg/kg) n=27948_**	**Ibuprofen (10mg/kg) n=27837**
Acute gastrointestinal bleeding	0	2	2
Abdominal pain	0	4	
Asthma	24	44	
Leukopenia	0	4	4
Erythema multiforme	1	1	2
Scalded Skin Syndrome	0	1	0
Serum Sickness	1	0	0

Hemiparesis,	0	0	1
Vomiting/gastritis	6	20	

Table: Risk of Hospitalization with Selected Discharge Diagnosis Judged as Possibly Drug Related According to Antipyretic Assignment

Assessor's comment:
In this context no special safety conclusion is drawn by the Boston University Fever Study concerning the subgroup analysis of children less than two years of age. However the risk of hospitalization with an acute gastrointestinal bleed is considered interesting concerning the subgroup children less than two years of age who were randomized to ibuprofen, the risk of hospitalization with an acute gastrointestinal bleed was 17 per 100,000 (95% confidence interval, 3.5 to 49 per 100,000); but this risk did not vary significantly by ibuprofen dose, nor was it significantly greater than the corresponding risk among children randomized to receive acetaminophen (0 per 9,127; 95% confidence interval, 0 to 33 per 100,000) (Fisher's exact test, p=0.6). Among children two years and older randomized to ibuprofen, the risk of hospitalization with an acute gastrointestinal bleed was 2.6 per 100,000 (95% confidence interval, 0.05 to 15 per 100,000); this risk was not significantly greater than the corresponding risk among children randomized to acetaminophen (0 per 19,003; 95% confidence interval, 0 to 16 per 100,000). Among children randomized to ibuprofen, the risk of hospitalization with an acute gastrointestinal bleed did not vary significantly by age (Fisher's exact test, p=0.1).

Overview of Periodic Safety Update Reviews
This Periodic Safety Update Report (PSUR) for ibuprofen (and its salt ibuprofen lysinate) summarises the safety data obtained by the Company from worldwide sources including data received from licensing partners for the reporting period of 01 January 2005 to 09 June 2010 and was examined for compatibility with the RSI, which is the German SmPC, to ensure any necessary amendments in relation to paediatric usage had been incorporated into the SmPCS. The review of the medically confirmed and medically unconfirmed safety data received during the period covered by this PSUR did not identify any new safety issues that alters the benefit-risk profile of the active moiety.

Assessor's comment:
According to the MAH the data are in line with the safety profile outlined in the RSI and/or reflect the background incidence in the target population and the favourable risk-benefit balance of ibuprofen (and its salt ibuprofen lysinate) is demonstrated, when used as directed.

<u>The submission of Pfizer contains:</u>

Literature review:
The MAH conducted a literature search from January 2008 to October 2010 in Medline to identify additional relevant paediatric studies as an update to a previous literature review of ibuprofen submitted in January 2008. Including two meta-analyses of the efficacy and safety of ibuprofen in paediatric populations (Pierce, 2010; Southey, 2009) which were identified by the MAH.

Assessor's comment:
The literature review does not provide new information about the use of ibuprofen in children and adolescents.
No consequential regulatory action is taken into consideration according to the literature review.

Clinical studies:
Clinical studies conducted in paediatric subjects/patients are summarized in the next subsection "2. Clinical Studies" in tabular format.

Also included in this summary table are studies in dental pain, migraine headache pain, tension headache pain and safety studies, which were not designed as paediatric studies but enrolled a small number of patients aged 12 years or older. The safety data from the patients aged 12 years or older are similar to those in the adult study populations. No serious adverse events were reported in these studies.

Assessor's comment:
The abovementioned studies were not designed as paediatric studies but enrolled a small number of patients aged 12 years or older.

Indications studied:
• D*ental pain:* 'Symptomatic treatment of mild to moderate pain e.g. dental pain' is a generally approved indication.

• *Migraine headache:* In the studies investigating migraine headache adolescents of at least 12 years and adults were included. However, in study AM-98-01 and in another study listed below the single dose of 600 mg ibuprofen was also investigated. Generally (for OTC use in DE) the 400 mg ibuprofen dose is the recommended maximum single dose for the symptomatic treatment of mild to moderate pain including migraine headache. In these studies the 600 mg single dose could not show a more favourable effect in comparison to the 400 mg single dose of ibuprofen.

• *Tension headache pain:* In one study researching tension headache pain in adolescents from 14 years and adults no separation relating to the adolescent age group from14 to 17 years was given. Therefore, the study results cannot be easily interpreted for this adolescent age group.

Safety:
• No modified conclusions concerning ibuprofen in the paediatric population can be drawn according to the safety studies.

Randomised, controlled, blinded, clinical trials were conducted exclusively in paediatric subjects ranging from 6 months to 14 years of age. These studies were conducted in trials for indications of fever reduction (antipyresis) or pain relief. In many of these studies ibuprofen demonstrated superior efficacy compared to placebo or active comparator (paracetamol).

Assessor's comment:
The indication 'symptomatic treatment of fever' is an approved indication of ibuprofen in children and adolescents. Changes are not necessary. No changes are considered necessary with respect to the approved indication 'symptomatic treatment in mild to moderate pain' for ibuprofen.

Remaining studies were conducted for pain relief from various conditions (earache, sore throat pain) and from orthodontic separator placement.

PSUR:

The safety of ibuprofen was recently reviewed in two 1-year Periodic Safety Update Reports (PSURs) covering the reporting time periods of 02 September 2008 to 01 September 2009 (PSUR 1) and 02 September 2009 to 01 September 2010 (PSUR 2). The information contained in these 2 PSURs supports the known safety profile of ibuprofen in the paediatric population. The new safety issue relating to hypovolemia and acute renal failure in paediatric patients has been addressed through revision of the ibuprofen RSI for products intended for use in children under 12 and the corresponding product information is in the process of being updated to appropriately inform patients of this safety risk.

2. Clinical studies

Johnson & Johnson:

Tabular listing of clinical studies [unpublished with ibuprofen in paediatric population only]

Type of Study	Study identifier	Objective(s) of the Study	Study Design and Type of Control	Age range	Treatment(s); Dosage Regimen; Form; Route	Number of subjects	Patient Diagnosis	Duration of treatment	Study status; Type of Report	Compatible with SmPC
Efficacy	(80) 1988	comparing the efficacy and safety of ibuprofen elixir (6 - 7 mg/kg) and acetaminophen elixir (10 - 15 mg/kg) in febrile children	Randomized, Double Blind, Multi-center, Parallel	> 6 m - < 6 y	IBU 6-7 mg/kg [a] APAP 10-15 mg/kg [b]	49	Children with a rectal temperature ≥ 101°F (=38.3°C) and 104.9°F (=40.5°C)	single dose	Completed; abbreviated	Compatible with SmPC.
Efficacy	(84) 1988	Comparing the antipyretic efficacy and safety of ibuprofen at 3 mg/kg, 6 mg/kg, and 9 mg/kg with Children's TYLENOL@ (acetaminophen) Elixir, at 12 mg/kg, in febrile children	Randomized, Open-label, Multi-center, Parallel	> 6 m - < 6 y	Ibuprofen Group 1 3 mg/kg Group 2 to app. 6 mg/kg. Group 3 to app. 9 mg/kg. Acetaminophen Group 4 to app. 12 mg/kg	126	Children (7.0 kg to 26.9 kg) with a rectal temperature ≥ 101°F (=38.3°C) and 104.9°F (=40.5°C) for 6m-3y and ≥ 101°F (=38.3°C) and 103.9°F (=39.9°C) for 4y-6y	single dose	Completed; abbreviated	Lowest dose outside dose range, otherwise compatible with SmPC.
Efficacy	(85) 1988	Comparing the efficacy and safety of 5 - 7 mg/kg of ibuprofen and 10 - 15 mg/kg of acetaminophen in febrile children.	Randomized, Double Blind, Multi-center, Parallel	> 6 m - < 12y	Ibuprofen 5-7 mg/kg q4h up to 4 days Acetaminophen 10-15 mg/kg. q4h up to 4 days	386	Children with an acute febrile illness. Children 6 m to 3 y with a baseline rectal temperature ≥ 102°F (=38.9°C) and ≤ 104.9°F (=40.5°C) , and children 4-11 y with a baseline oral temperature ≥ 101°F (=38.3°C) and ≤ 103.9°F (=38.3°C)	4 days or recovery	Completed; abbreviated	Compatible with SmPC.
PK/PD	(106) 1989	Evaluation of the antipyretic efficacy, safety, and blood levels of ibuprofen 6 mg/kg. Acetaminophen 10-15 mg/kg was used as a positive control for efficacy	Randomized, Open-label, Multi-center, Parallel	> 6 m - < 12y	Ibuprofen 6 mg/kg Acetaminophen 10-15 mg/kg.	43	Children with oral temperatures between 101°F (=38.3°C) and ≤ 103.9°F (=38.3°C) or rectal temperatures between 102°F (=38.9°C) and 104.9°F (=40.5°C)	Single Dose	Completed; abbreviated	Compatible with SmPC.

Efficacy	(136) 1990	Comparing efficacy and side effects profile of various ibuprofen doses with APAP 10-15 mg/kg as a reference	Randomized, Single Blind, Multi-center, Parallel	not given	Single dose Ibuprofen 3mg/kg Ibuprofen 6mg/kg Ibuprofen 9mg/kg APAP 10-15 mg/kg	36	Febrile children; no further details given	single dose	discontinued	Lowest dose outside dose range, otherwise compatible with SmPC.
Efficacy	(149) 1991	Comparing for eight hours the efficacy and side effects profile of acetaminophen elixir 12.5 mg/kg and 25 mg/kg and ibuprofen suspension 5 mg/kg and 10 mg/kg in the treatment of febrile children.	Randomized, Double Blind, Multi-center, Parallel	2-11 years	Single dose APAP 12.5 mg/kg APAP 25 mg/kg Ibuprofen 5 mg/kg Ibuprofen 10 mg/kg	275	Children with an acute febrile illness of ≥ 6 h duration. ≥102.0°F to ≤ 105.5°F rectally in children two years through three years old (24-47 months) ≥101.0°F to ≤104.5°F orally in children four years through eleven years old.	single dose	Completed; abbreviated	Compatible with SmPC.
Efficacy	(155) 1992	Evaluation and comparison the efficacy and side effects profile of single doses of acetaminophen elixir 10-15 mg/kg and ibuprofen suspension 5 mg/kg and 10 mg/kg over an eight-hour period in the treatment of febrile children.	Randomized, Double Blind, Multi-center, Parallel	2-11 years	Single dose APAP 10-15 mg/kg Ibuprofen 5 mg/kg Ibuprofen 10 mg/kg	219	Children with an acute febrile illness of ≥ 6 h duration. Baseline temperature ≥ 101°F and ≤ 104.5°F orally in children 4-11 y, or ≥ 102°F and ≤ 105.5°F rectally in children 2-3 y	single dose	Completed; abbreviated	Compatible with SmPC.
Efficacy	(161) 1992	Comparison the efficacy and safety of ibuprofen suspension dosed at 5 and 10 mg/kg to acetaminophen elixir dosed at 12.5 mg/kg and to placebo in the treatment of acute ear pain due to acute otitis media in children	Randomized, Double Blind, Placebo-Controlled, Multi-center, Parallel	4-13 years	APAP 12,5 mg/kg Ibuprofen 5 mg/kg Ibuprofen 10 mg/kg placebo	158	Children with an acute illness in which a sore or painful ear was a prominent symptom, and with signs of acute suppurative otitis media	single dose	Completed; abbreviated	Compatible with SmPC.
Efficacy	(162) 1992	Comparison the efficacy and safety of a single dose of ibuprofen suspension dosed at 5 and 10 mg/kg to acetaminophen elixir dosed at 12.5 mg/kg and to placebo in the treatment of acute sore throat pain believed due to an infectious agent in children.	Randomized, Double Blind, Placebo-Controlled, Multi-center, Parallel	5-12 years	APAP 12,5 mg/kg Ibuprofen 5 mg/kg Ibuprofen 10 mg/kg placebo	260	Children with an acute illness in which at least moderately sore or painful throat was a prominent symptom which had been present for 6 to 72 h prior to study entry.	single dose	Completed; abbreviated	Compatible with SmPC.
PK/PD	(167S) 1994	Evaluation and comparison of the antipyretic. efficacy, the side effects profile, and the blood levels of·a new ibuprofen chewable tablet preparation to marketed ibuprofen suspension (Children's Motrin ibuprofen suspension) in febrile children.	Randomized, Open-label, Multi-center, Parallel	2-11 years	Tablet: Ibuprofen 5 mg/kg Ibuprofen 10 mg/kg Suspension. Ibuprofen 5 mg/kg Ibuprofen 10 mg/kg	83	Children 2-11 y with an acute febrile illness of ≥ 6 h duration. Baseline temperature ≥ 101°F and ≤ 104.5°F orally, or ≥ 102°F and ≤ 105.5°F rectally.	single dose	Completed; abbreviated	Compatible with SmPC.

Efficacy	(206) 1995	To assess the antipyretic efficacy and safety profile of a single dose of ibuprofen chewable tablets (50 mg) and ibuprofen suspension (100 mg/5cc) dosed at approximately 5 mg/kg and 10 mg/kg in the treatment of febrile children two through 11 years old.	Randomized, Double Blind, double-dummy design Multi-center, Parallel	2-11 years	Tablet: Ibuprofen 5 mg/kg buprofen 10 mg/kg Suspension. Ibuprofen 5 mg/kg Ibuprofen 10 mg/kg	227	Children aged two to 11 years old with temperature from 101.0 of to 104.5 OF orally or 102.0 o F to 105.5°F rectally.	single dose	Completed; integrated, full	Compatible with SmPC.
Efficacy	(257) 2000	To evaluate and compare the antipyretic efficacy over an 8 hour period of acetaminophen suspension (160 mg/5 mL) (Children's Tylenol) at a dose of 12.5 mg/kg (10-15 mg/kg) given at hours 0 and 4 with ibuprofen suspension (100 mg/5 mL) (Children's Motrin) at a dose of 7.5 mg/kg (6.3-9.4 mg/kg)-given at hour 0 in the treatment of febrile children. To evaluate and compare the safety profile of these two products.	randomized, parallel, multiple dose, double-blind, multicenter study	2-11 years	APAP 12.5 mg/kg Ibuprofen 7. 5 mg/kg	280	age between 2 through 11 years and the presence of an acute febrile illness with temperature between 101.0°F to 104.5°F orally or 102.0°F to 105.5°F rectally	8 hours	Completed; integrated, full	Compatible with SmPC.
Efficacy	(256) 2000	Evaluation and comparison of the antipyretic efficacy of a single dose of ibuprofen suspension (Children's Motrin®) (100 mg/5 ml) at a dose of 7.5 mg/kg with the efficacy of a single dose of acetaminophen suspension (Children's Tylenol®) (160 mg/5 ml) at a dose of 12.5 mg/kg (10-15 mg/kg) in the treatment of febrile children, to evaluate and compare the rate of temperature reduction of these products, and to evaluate and compare the safety profiles of these products	randomized, parallel, single-dose, double-blind, multicenter study	1-11 years	Ibuprofen 7.5 mg/kg Acetaminophen 12.5 mg/kg.	110	Subjects with oral temperatures between 101.0°F to 104.5°F or rectal temperatures between 102.0°F to 105.5°F were enrolled. Qualified subjects were stratified into two groups: High Fever (>102.5°F) or Low Fever (£102.5°F)..	single dose	Completed; integrated, full	Compatible with SmPC.
Efficacy	(187) 1995	To evaluate the efficacy and side effects of a single dose of ibuprofen suspension dosed at 5 mg/kg or 10 mg/kg compared to placebo in the treatment of acute post-operative pain due to either inguinal herniorrhaphy in males, or umbilical herniorrhaphy in males and females, ages 5 through 11 years.	Randomized, Double Blind, Placebo-Controlled, Multi-center, Parallel	5-11 years	Single dose placebo Ibuprofen 5 mg/kg Ibuprofen 10 mg/kg	45	Age of 5 and 11 within a weight range of 35 to 119 pounds. Same day surgery for either unilateral or bilateral inguinal herniorrhaphy or umbilical herniorrhaphy	single dose	Dis-continued	Compatible with SmPC.

Efficacy	(214) 1996	Evaluation and comparison of the antipyretic efficacy of a single dose of ibuprofen suspension at a dose of 7.5 mg/kg with acetaminophen suspension at a dose of 12.5 mg/kg in the treatment of febrile children; Evaluation and comparison of the safety profiles of the two treatments.	randomized, parallel, single-dose, investigator-blinded, multi-center study	2-11 years	APAP 12.5 mg/kg Ibuprofen 7. 5 mg/kg	111	Acute febrile illness, between the ages of 2 years through 11 years old, and within a weight range of 24-95 lb. (11-43.9 kg).	single dose	Completed; integrated, full	Compatible with SmPC.
Efficacy	(190) 1994	Evaluation and comparison of the antipyretic efficacy and the side effect profiles of acetaminophen sustained release pediatric chewable tablets dosed at 20 to 30 mg/kg and a marketed ibuprofen suspension (Children's Motrin® ibuprofen suspension) dosed at 5 mg/kg and 10 mg/kg in the treatment of ambulatory febrile children	multi-center, randomized, single-dose, double-blind, parallel study	2-11 years	Single dose APAP 20-30 mg/kg as extended release chewable tablet (160mg) or Ibuprofen 5 mg/kg Ibuprofen 10 mg/kg suspension	218	Patients with acute febrile illness stratified in low fever group (101.0o - F102.5° F orally) or the high fever group (> 102.5° F-104.5° F orally). , between the ages of 2 through 11, and were within a weight range of 24-95 pounds (11 - 43 kg),	single dose	Completed; integrated, full	Compatible with SmPC.
Efficacy	(226) 1997	Evaluation and comparison of the antipyretic efficacy of a single dose of ibuprofen suspension at a dose of 7.5 mg/kg with acetaminophen suspension at a dose of 12.5 mg/kg in the treatment of febrile patients and to evaluate and compare the safety profiles of these treatments.	randomized, investigator-blinded, multi-site, parallel study	1-11 years	APAP 12.5 mg/kg Ibuprofen 7. 5 mg/kg	74	Acute febrile illness, ages between 2 years through 11 years, and within a weight range of 24-95 lb. (11-43.9 kg), and the 5-95th percentiles for weight and height based on age and sex	single dose	Completed; abbreviated	Compatible with SmPC.
PK	(CPR - 149) 1999	(I) Determination of the multiple-dose pharmacokinetics of ibuprofen and pseudoephedrine in children when both drugs are administered in combination as a suspension and (II) to assessment of the potential for a drug-drug pharmacokinetic interaction by comparing the results with those from previous single-ingredient studies in children.	open-label and multiple-dose design	4-11 years	7.5 mg/kg of ibuprofen and 1.125 mg/kg of pseudoephedrine HCl per dose; one dose of ibuprofen-pseudoephedrine HCl suspension given every six hours for five doses.	24	Healthy children ages four through 11 years	five doses of sus-pension over two days	Completed; integrated, full	Compatible with SmPC.

Safety	(231) 1993	Conduction of a practitioner-based, randomized, double-blind, acetaminophen-controlled study that would provide valid, stable, and clinically relevant information on the occurrence of rare but serious events among ibuprofen-exposed children relative to those exposed to acetaminophen.	randomized, double-blind, multicenter, parallel study	0.5 - 12 years	acetaminophen 12 mg/kg ibuprofen 5 mg/kg; ibuprofen 10 mg/kg	8419 2	febrile children ranging in weight from 15 to 109 pounds(but no less than 6 months of age and no more than 12 years of age)	no limit	Completed; integrated, full	Compatible with SmPC.
Safety	(231(S1)) 1997	Description of the risk of serious adverse clinical events following antipyretic use among a subgroup of children less than two years of age by subanalysis of the 'Boston Fever Study'.	randomized, double-blind, multicenter, parallel study	0.5 - 2 years	acetaminophen 12 mg/kg; ibuprofen 5 mg/kg; ibuprofen 10 mg/kg	2706 5	febrile children ranging in weight from 15 to 109 pounds(but no less than 6 months of age and no more than 2 years of age)	no limit	Completed; abbreviated	Compatible with SmPC.
Safety	(239 R1) 1999	Description of the safety profile of a pediatric combination suspension product containing ibuprofen and pseudoephedrine HCl in children two through 11 years of age, weighing 24 to 95 pounds, who had symptoms of the common cold, the flu, or sinusitis.	multicenter, open-label study	2 - 11 years	every six to eight hours 6.6mg/kg IBU +1mg/kg PSE - 10mg/kg IBU+1.5mg/kg PSE of a suspension with 100 mg of ibuprofen and 15 mg of pseudoephedrine HCl per 5 mL	114	children (2 - 11 years) with symptoms of the common cold, the flu or sinusitis	3 days or recovery	Completed; integrated, full	Combi-nation product - Not compatible with SmPC.
Efficacy	272 (2003)	The primary objective was to determine whether the efficacy of co-administered doses of ibuprofen and pseudoephedrine HCl in the treatment of primary nocturnal enuresis was greater than that for the respective dose of each drug alone. The secondary objective was to determine whether the individual drugs were each effective compared with placebo.	Double-blind, double-dummy, placebo-controlled, randomized, parallel-group, multiple-center	6 - 11 years	12.5 mg/kg ibuprofen suspension and 15 or 30mg pseudoephedrine HCl suspension; 12.5 mg/kg ibuprofen and of placebo . 15 or 30 mg pseudoephedrine HCl suspension and placebo. 2 placebos	318	Healthy male and female subjects, ages six through 11 years with primary nocturnal enuresis	14 days	Completed; integrated, full	Combi-nation product: new indication- Not compatible with SmPC.

Assessor's comment:
Concerning these reports please refer for evaluation to the preceding subsection 1 above.

Tabular listing of clinical studies [unpublished with ibuprofen in adults and some persons < 18 years]

Type of Study	Study identifier	Objective(s) of the Study	Study Design and Type of Control	Age range	Treatment(s); Dosage Regimen; Form; Route	Number of subjects	Patient Diagnosis	Duration of treatment	Study status; Type of Report	Compatible with SmPC
Efficacy	(51) 1984	Evaluation of the relative analgesic efficacy and safety of APAP 650 mg, ibuprofen 200 mg, and placebo in pain intensity and pain relief	Randomized, Double Blind, Placebo-Controlled, Single Investigator, Parallel	Not given	Capsules containing : APAP 650 mg IBU 200 mg placebo	68F, 58M	Subjects ≥ 16 y with moderate to severe pain following oral surgery	Single-dose, 4 hours	Completed; abbreviated	Compatible with SmPC
Efficacy	(52) 1984	Evaluation of the relative analgesic efficacy and safety of APAP 1000 mg, ibuprofen 200 mg and 400 mg, and placebo in pain intensity and pain relief	Randomized, Double Blind, Placebo-Controlled, Single Investigator, Parallel	Not given	Capsules containing : APAP 1000 mg IBU 200 mg IBU 400 mg placebo	92F, 63M	Subjects ≥ 16 y with moderate to severe pain following oral surgery	Single-dose, 6 hours	Completed; abbreviated	Compatible with SmPC
Efficacy	(58) 1985	Evaluation of the relative analgesic efficacy and safety of APAP 1000 mg, ibuprofen 200 mg and 400 mg, and placebo in pain intensity and pain relief	Single-dose, double-blind, placebo-controlled, fully randomized, parallel study, multi-center	Not given	Capsules containing : APAP 1000 mg IBU 200 mg IBU 400 mg placebo	86F, 72F	Subjects ≥ 16 y with moderate to severe pain following oral surgery	Single-dose, 6 hours	Completed; abbreviated	Compatible with SmPC
Efficacy	(60) 1985	Comparison of the efficacy and safety of acetaminophen 1000 mg, ibuprofen 200 mg, ibuprofen 400 mg, and placebo in the treatment of pain following removal of impacted third molars	Single-dose, double-blind, placebo-controlled, fully randomized, parallel study, multi-center	Not given	Capsules containing : APAP 1000 mg IBU 200 mg IBU 400 mg placebo	20y 70F, 50M	Subjects ≥ 15 y with moderate to severe pain followingremoval of impacted third molars.	Single-dose, 6 hours	Completed; abbreviated	Compatible with SmPC
Efficacy	(66) 1986	Comparison of the efficacy and safety of acetaminophen 1000 mg, ibuprofen 200 mg, ibuprofen 400 mg, and placebo in the treatment of pain following periodontal surgery.	Randomized, Double Blind, Placebo-Controlled, Single-Investigator,	Not given	Capsules containing : APAP 1000 mg IBU 200 mg IBU 400 mg placebo	mean: > 42 y and < 48y 76F, 47M	Subjects ≥ 16 y with moderate to severe pain following periodontal surgery.	Single-dose, 6 hours	Completed; abbreviated	Compatible with SmPC

			Parallel							
Efficacy	(67) 1986	Comparison of the efficacy and safety of acetaminophen 650 mg, ibuprofen 200 mg, , and placebo in the treatment of pain following oral surgery.	Randomized, Double Blind, Placebo-Controlled, Multi-Clinic, Parallel	Not given	capsulEs containing : APAP 650 mg IBU 200 mg placebo	mean: > 42 y and < 48y 95F, 46M	Subjects ≥ 16 y with moderate to severe pain following oral surgery.	Single-dose, 4 hours	Completed; abbreviated	Compatible with SmPC
Efficacy	(73) 1986	The objective of this study is to compare the effects of acetaminophen (APAP) 1000 mg four times a day (4 grams daily dose) and Ibuprofen 400 mg three times a day (1200 mg daily dose) and placebo in the treatment of primary dysmenorrhea.	Three-trial three-treatment (APAP, Ibuprofen and placebo) crossover study. randomized to one of the six possible sequences) and were assigned the corresponding drug for three successive menstrual cycles..	Not given	Capsules containing : APAP 1000 mg IBU 400 mg placebo for maximum of APAP 4000 mg IBU 1200 mg	Ø 28.6 y	Female patients between 16 and 45 years with regular menstrual cycles who have a history of recurrent moderate to severe dysmenorrhea, which requires drug therapy .	Up to 4 days	Completed; abbreviated	Compatible with SmPC
Efficacy	(77) 1987	Comparison of the safety and analgesic efficacy of Acetaminophen (APAP) 1000 mg, Ibuprofen 400 mg, Ibuprofen 200 mg, and Placebo in the treatment of tension headache.	Randomized, Double Blind, Placebo-Controlled Multi-Clinic Parallel	16 – 82 years	Capsules containing : APAP 1000 mg IBU 200 mg IBU 400 mg placebo	Ø31.5 y (16 y – 82 y) 805F, 316M	Subjects ≥16 years with a history of acute tension headache at least once a week	Single dose	Completed; abbreviated	Compatible with SmPC
Efficacy	(81) 1987	Comparison of the analgesic efficacy of aspirin 1000 mg/caffeine 64 mg, ibuprofen 400 mg, and placebo	Randomized, Double Blind, Parallel, Placebo-Controlled, Single Investigator	Not given	Capsules containing : Aspirin 1000 mg/ caffeine 64 mg Ibuprofen 400 mg Placebo	mean ~25y 65F, 58M	Subjects ≥ 16 y with at least moderate pain following third molar extraction	Single dose	Completed; abbreviated	Compatible with SmPC

Efficacy	(87) 1988	Comparison of the analgesic efficacy of aspirin 800 mg/caffeine 64 mg, ibuprofen 400 mg, and placebo	Randomized, Double Blind, Parallel, Placebo-Controlled, Single Investigator	Not given	Capsules containing : Aspirin 800 mg/ caffeine 64 mg Ibuprofen 400 mg Placebo	mean ~25y 61F, 63M	Subjects ≥ 16 y with at least moderate pain following third molar extraction.	Single dose	Completed; abbreviated	Compatible with SmPC
Efficacy	(92) 1988	Comparison of the analgesic efficacy and side effects of aspirin 1000 mg/caffeine 64 mg, ibuprofen 400 mg, and placebo	Randomized, Double Blind, Parallel, Placebo-Controlled, Single Investigator	Not given	Capsules containing : Aspirin 1000 mg/ caffeine 64 mg Ibuprofen 400 mg Placebo	mean ~24y 62F, 57M	Subjects ≥ 16 y with at least moderate pain following third molar extraction	Single dose	Completed; abbreviated	Compatible with SmPC
Efficacy	(93) 1989	Comparison of the efficacy and side effects of an ibuprofen 400 mgjpseudoephedrine 60 mg dosage, an ibuprofen 200 mgjpseudoephedrine 30 mg dosage, and placebo in the treatment of sinus headache	Randomized, Double Blind, Placebo Control, Parallel, Multi-Clinic	16 y - 83 y	IBU 400 mg +PSE 60 mg IBU 200 mg +PSE 30 mg placebo	mean ~40y 138F, 44M	Subjects age 16 y or older diagnosed as having repeated episodes of acute sinus headaches of sufficient severity to require treatment	Single dose 6 hours	Completed; abbreviated	Combination product – not compatible with SmPC
Efficacy	(94) 1988	Comparison of the efficacy and side effects of an ibuprofen 400 mg + pseudoephedrine 60 mg dosage, an ibuprofen 200 mg + pseudoephedrine 30 mg dosage, and placebo in the treatment of sinus headache.	Randomized, Double Blind, Placebo Control, Parallel, Multi-Clinic	(16 y - 66 y)	IBU 400 mg +PSE 60 mg IBU 200 mg +PSE 30 mg placebo	mean ~34y 78F, 36M	Subjects age 16 y or older diagnosed as having repeated episodes of acute sinus headaches of sufficient severity to require treatment	Single dose 6 hours	Completed; abbreviated	Combination product – not compatible with SmPC
Efficacy	(95) 1988	Evaluation and comparison of efficacy of the treatments in acute Sinus Headache (pain and congestion)	Randomized, Double Blind, Placebo Control, Parallel, Multi-Clinic	(16 y - 76 y)	IBU 400 mg +PSE 60 mg IBU 200 mg +PSE 30 mg placebo	100F, 28M	Patients ≥ 16 y with repeated episodes of acute sinus headaches of sufficient severity to require treatment.	Single dose 6 hours	Completed; abbreviated	Compatible with SmPC
Efficacy	(97) 1988	Comparison of the efficacy of ibuprofen 200 mg, ibuprofen 200 mg plus caffeine 100 mg, ibuprofen 400 mg, ibuprofen 400 mg plus caffeine 200 mg, caffeine 100 mg, and placebo in the treatment of pain following third molar extraction.	Randomized, Double Blind, Parallel, Placebo-Controlled, Single Investigator	Not given	Tablets with: IBU 200 mg IBU 200 mg plus Caffeine 100 mg IBU 400 mg IBU 400 mg plus Caffeine 200 mg Caffeine 100 mg Placebo	mean ~25y 157F, 140M	Subjects ≥ 16 y with moderate to severe pain secondary to removal of impacted third molars.	Single-dose, 8 hours	Completed; abbreviated	Severe pain not listed otherwise compatible with SmPC

Efficacy	(103) 1989	Comparison of the analgesic efficacy and side effects of aspirin 1000 mg/caffeine 64 mg, ibuprofen 400 mg, and placebo	Randomized, Double Blind, Placebo-Controlled, Parallel, Single Investigator	Not given	Capsules containing : Aspirin 1000 mg/ caffeine 64 mg Ibuprofen 400 mg Placebo	mean ~24y 67F, 51M	Subjects ≥ 16 y with at least moderate pain following third molar extraction.	Single-dose, 4 hours	Completed; abbreviated	Compatible with SmPC
Efficacy	(111A) 1989	Comparison of the efficacy of ibuprofen 200 and 400 mg to ibuprofen/caffeine combinations of 200/100 and 400/200 mg respectively, and to caffeine 100 mg and placebo in the treatment of pain after orthopaedic surgery	Randomized, Double Blind, Parallel, Placebo-controlled, Multi-Clinic	Not given	Tablets with: IBU200 mg IBU200 mg/Caffeine 100 mg IBU400 mg IBU400 mg/Caffeine 200 mg Caffeine 100 mg Placebo	mean >35 and<39y 159F, 217M	Subjects ≥ 16 y with moderate to severe pain secondary to an orthopaedic surgical procedure	Single-dose, 8 hours	Completed; integrated, full	Pain after orthopaedic surgery not specifically listed otherwise compatible with SmPC
Efficacy	(112) 1989	Comparison of the efficacy of ibuprofen 200 and 400 mg to ibuprofen/caffeine combinations of 200/100 and 400/200 mg respectively, and to caffeine 100 mg and placebo in the treatment of pain following third molar extraction.	Randomized, Double Blind, Parallel, Placebo-controlled, Multi-Clinic	Not given	Tablets with: IBU200 mg IBU200 mg/Caffeine 100 mg IBU400 mg IBU400 mg/Caffeine 200 mg Caffeine 100 mg Placebo	mean >24 and<26y 163F, 122M	Subjects ≥ 16 y with moderate to severe pain secondary to third molar extraction	Single-dose, 8 hours	Completed; integrated, full	Severe pain not listed otherwise compatible with SmPC
Efficacy	(116) 1990	Evaluation and comparison of the safety and efficacy of 600 mg ibuprofen sustainedrelease to 200 mg ibuprofen regular release administered every four hours and placebo in patients with moderate to severe pain secondary to the surgical extraction of impacted third molars.	Randomized, Double Blind, Parallel, Placebo-controlled, Multi-Clinic	(16 – 38 y)	Tablets with: IBU 200 mg q4h [a] IBU SR 600 mg Placebo	mean ~24y 70F, 59M	Subjects age 16 y or older with moderate to severe pain following extraction of impacted third molars.	Single/ multidose	Completed; integrated, full	Severe pain not listed otherwise compatible with SmPC
Efficacy	(119) 1990	Evaluation and comparison of the safety and efficacy of 600 mg ibuprofen sustained release to 200 mg ibuprofen regular release administered every four hours and placebo in patients with moderate to severe pain secondary to the surgical extraction of impacted third molars.	Randomized, Double Blind, Parallel, Placebo-controlled single center	(16 – 46 y)	Tablets with: IBU 200 mg q4h [a] IBU SR 600 mg Placebo	mean ~24y 75F, 29M	Subjects ≥ 16 y with at least moderate pain following third molar extraction.	Single/ multidose	Completed; integrated, full	600 mg Dose – not compatible with SmPC

Efficacy	(122) 1990	Evaluation and comparison of efficacy and side effects profile of single doses of ibuprofen 200 mg and 400 mg, naproxen 200 mg and 400 mg, and placebo over an eight-hour period when administered to oral surgery patients with moderate to severe pain following third molar extraction.	Randomized, Double Blind, Placebo-Controlled, Multi-Clinic, Parallel	(16 y – 45 y)	Capsules with: Ibuprofen 200 mg Ibuprofen 400 mg Naproxen 200 mg Naproxen 400 mg Placebo	mean ~23y 99F, 95M	Subjects age 16 y or older with moderate to severe pain following third molar extraction.	Single dose	Completed; abbreviated	Severe pain not listed otherwise compatible with SmPC
Efficacy	(128S) 1992	Determination of the safety and efficacy of ibuprofen sustained release 600 mg administered twice daily and ibuprofen regular release 400 mg administered three times daily versus placebo in the treatment of primary dysmenorrhea.	Randomized, Double Blind, Crossover, Multi-Clinic, Placebo-Controlled	(17 y - 45 y)	IBU SR 600 mg bid 4 days caplet oral; IBU 400 mg tid 4 days caplet oral; Placebo tid 4 days	mean ~24y 122F	Females between the ages of 16 and 45 years. Patients should have had regular menstrual cycles and a history of recurrent moderate to severe dysmenorrhea	Multidose TID for 4 days	Completed; abbreviated	Severe pain not listed otherwise compatible with SmPC
Efficacy	130S) 1992	The objective of this study was to determine the safety and efficacy of ibuprofen sustained release 600 mg administered twice daily and ibuprofen regular release 400 mg administered three times daily versus placebo in the treatment of primary dysmenorrhea.	double-blind, randomized, placebo controlled, three period crossover study	(16 y - 45 y)	1200 mg daily as: Ibuprofen Extended Release 600 mg; 3 x Ibuprofen Regular Release 400 mg caplet; placebo	69F	Women age 16 to 45 y with regular menstrual cycles with a history of recurrent moderate to severe dysmenorrhea with at least moderate lower abdominal pain.	Multidose TID for 4 days	Completed; abbreviated	600 mg Dose – not compatible with SmPC
Efficacy	(201) 1995	Evaluation and comparison of the safety and efficacy of a single dose of 600 mg ibuprofen sustained release to a single dose of 200 mg ibuprofen regular release and to a single dose of placebo in the treatment of pain secondary to post-operative foot surgery.	Randomized, Double Blind, Placebo-Controlled, Parallel, Multi-Clinic	(17 y– 83 y)	IBU 200 mg IBU SR 600 mg Pbo	mean ~46y 135F, 23M	Subjects age ≥ 16 y with moderate to severe pain secondary to foot surgery.	Single dose	Completed; abbreviated	Severe pain and , pain after surgery not listed otherwise compatible with SmPC
Efficacy	211) 1995	Evaluation of the onset of analgesia of single doses of ibuprofen chewable 400 mg, ibuprofen suspension 400 mg/20 ml, and placebo over a three hour period when administered to study subjects with moderate to severe post operative dental pain secondary to third molar extraction.	Randomized, double-blind, double-dummy, single-center, parallel, placebo controlled study	(16 – 48 y)	IBU chewable tablets (100 mg x four tablets) IBU suspension (100 mg/5 ml) Placebo	23,8 127F, 74M	Patients with moderate to severe pain secondary to third molar extraction	single dose, 3 hours	Completed; integrated, full	Severe pain not listed otherwise compatible with SmPC

Efficacy	(220) 1997	The overall objective of this study was' to evaluate over a 12 hour observation period the pharmacokinetic, pharmaco-dynamic, efficacy and safety profiles of a single dose of 600 mg ibuprofen extended release caplets compared to equivalent total doses of ibuprofen regular release 200 mg caplets administered in three different dosing regimens, and placebo in the treatment of moderate to severe post-operative dental pain	Double-blind, randomized, parallel, placebo-controlled, singlecenter	not given	Ibuprofen Extended Release 600 mg; 3 x Ibuprofen Regular Release 200 mg caplet; placebo	mean ~23y 122F, 88M	16 years of age or older, complaining of moderate to severe pain after extraction of three or four third molars	IBU ER 600 mg single dose at 0 hour IBU 600 mg single dose at 0 hour IBU 400 mg at 0 hour; 200 mg at 4 hours IBU 200 mg at 0,4, and 8 hours 12 hours	Completed; integrated, full	Severe pain not listed otherwise compatible with SmPC
Efficacy	(227) 1997	Evaluation of time to onset of meaningful relief	Randomized, Double Blind, Placebo-Controlled, Single Investigator, Parallel	(16 y – 47 y)	IBU 400mg magnetic therapy (=MagnaBlock) placebo	25.2 49F, 41M	Subjects with pain following third molar extraction	Single Dose	Completed; abbreviated	Compatible with SmPC
Efficacy	(232) 1998	Evaluation and comparison the analgesic characteristics (the onset and total analgesia) of single doses of an acetaminophen 1000 mg + dextromethorphan hydrobromide 30 mg combination to acetaminophen 1000 mg, dextromethorphan hydrobromide 30 mg, ibuprofen 400 mg and placebo over an eight-hour period when administered to subjects with moderate to severe postoperative dental pain secondary to extraction of three or four molars.	Single-dose, double-blind, placebo-controlled, fully randomized, parallel study	(16 y - 50 y)	Capsules containing : APAP 1000 mg + Dextro-methorphan hydro-bromide [DXM] 30 mg, . APAP 1000 mg, DXM 30 mg; ibuprofen 400 mg, placebo	mean ~22,6y 182F, 126M	Subjects ≥ 16 y with moderate to severe pain following the surgical extraction of three or four molars, at least one of which was an impacted third mandibular molar.	Single-dose, 8 hours	Completed; integrated, full	Compatible with SmPC

Efficacy	(242) 2000	Determination which combinations of ibuprofen and dextromethorphan hydrobromide have superior analgesic efficacy to the individual components alone.	Single-dose, double-blind, placebo-controlled, randomized study	(16 y - 51 y)	IBU 400 mg + dextromethorphan(= DMX) 40 mg ; IBU 400 mg + DMX 20 mg; IBU 400 mg + DMX 10 mg; IBU 200 mg + DMX 40 mg; IBU 200 mg + DMX 20 mg ; IBU 200 mg + DMX 10 mg; IBU 100 mg + DMX 40 mg; IBU 100 mg + DMX 20 mg; IBU 100 mg + DMX 10 mg; IBU 400 mg; IBU 200 mg; IBU 100 mg; DMX 40 mg; DMX 20 mg; DMX 10 mg; placebo.	mean 22,3y 372F, 269M	Patients with age ≥ 16 years and the presence of moderate to severe pain on a five-point scale after dental surgery involving the removal of three or four molars	Single dose 12 hours	(242) 2000	Combination product – not compatible with SmPC
PK/PD	(234) 2000	Evaluation over a 12 hour observation period of the pharmacokinetic (PK), pharmacodynamic (PD), efficacy and safety profiles of a single dose of 600 mg ibuprofen extended release caplets compared to equivalent total doses of ibuprofen regular release caplets (marketed OTC product), administered in divided doses every four hours, and placebo in the treatment of moderate to severe post-operative dental pain	Double-blind, randomized, parallel, placebo-controlled, single-center, PK/PD dental pain study	not given	Ibuprofen Extended Release 600 mg single dose Ibuprofen Regular Release 200 mg at 0, 4, and 8 hours Ibuprofen Regular Release 400 mg; 200 mg at 4 hours Ibuprofen Regular Release 600 mg single dose Placebo	197 mean ~24y 112F, 85M	Subjects ≥16 yr complaining of moderate to severe pain following the surgical extraction of three or four third molars	Single dose /repeat dose 12 hours	Completed; abbreviated	Compatible with SmPC
Efficacy	(261) 2000	Comparison of the overall analgesia of single doses of an acetaminophen / ibuprofen combination and ibuprofen alone over a six hour study period when administered to study subjects experiencing moderate to severe post-operative dental pain secondary to three or four molar extractions, with at least one being an impacted, third mandibular molar.	Randomized, double-blind, double-dummy, single-dose, single-center, parallel group pilot study	(16 y - 49 y)	Ibuprofen 200 mg / APAP 650 mg Combination Ibuprofen 400 mg	105 mean 24y 63F, 42M	Healthy subjects ≥ 16 years experiencing moderate to severe post-operative dental pain secondary to surgical extraction of three to four molars	single dose 6 hours	Completed; integrated, full	

Efficacy	(277) 2004	Comparison of the efficacy and safety of single doses of acetaminophen and ibuprofen when administered to study subjects experiencing moderate to severe postoperative dental pain	Randomized, single-dose, double-blind, double-dummy, placebocontrol led, parallel group study	(15y - 34y)	APAP 1000 mg ibuprofen 400 mg placebo	224 mean ~18y 110F, 114M	Subjects age 15 years or older experiencing moderate to severe pain following oral surgery of a minimum of three third molars	Single dose 4 hours	Completed; integrated, full	Severe pain not listed otherwise compatible with SmPC
Efficacy	(278) 2004	Comparison of the safety and efficacy of 1300 mg acetaminophen extended release (ER) given three times per day to that of 400 mg ibuprofen given three times per day for the treatment of the signs and symptoms of Grade I and Grade II lateral ankle sprains, when each product was administered for a total of nine days	Multicenter, randomized, double-blind, parallel-group, comparative study	(16 y - 73 y)	APAP SR 3900 mg per day IBU 1200 mg per day	260 mean 32,5y 147F, 113M	Patients 18 years or older with a Grade I or Grade II lateral ankle sprain according to the Leach Classification.	Multible dose 9 days	Completed; integrated, full	Treatment longer than in OTC, otherwise compatible with SmPC
Efficacy	(285) 2004	Comparison of the efficacy and safety of single doses of acetaminophen and ibuprofen when administered to study subjects experiencing moderate to severe postoperative dental pain	randomized, single-dose, double-blind, double-dummy, placebocontrol led, parallel group study	(15 y - 29 y)	Capsules containing : APAP 1000 mg IBU 400 mg placebo	222 mean 18y 119F, 103M	Subjects ≥15 years, weight ≥ 100 pounds, body mass index of 18 to 28 (inclusive), and the presence of moderate to severe. pain and a rating of at least 50 mm on a 100 mm visual analog scale (VAS) following the extraction of a minimum of three molars	single dose	Completed; integrated, full	Severe pain not listed otherwise compatible with SmPC
	TRAMAP·ANAG-012 CSR	Evaluation of the Efficacy and Safety of TrarnadollAPAP in Oral Surgical Pain	Randomized, double-blind, parallel-group, active-controlled factorialdesign trial with a placebo control	(15 y - 46 y)	TRAM/APAP TRAM 75 mg APAP 650 mg Ibuprofcn 400 mg Placebo.	400 mean 21,7y 221F, 179M	Healthy subjects 16 years of age or older. Moderate or severe pain (score of at least 5 on VAS) as a result of an oral surgical procedure.	Single dose 8 hours	Completed; integrated, full	Severe pain not listed otherwise compatible with SmPC

Efficacy	TRAMAP·ANAG-02 CSR	Evaluation of the efficacy and safety of the combination tramadol 75 mg (TRAM) with acetaminophen (APAP) 650 mg in subjects experiencing pain from oral surgical procedures and to demonstrate the contribution of each component to the effect of the combination.	Randomized, double-blind, parallel-group, factorial design trial with active control	(16 y - 48 y)	TRAM/APAP TRAM 75 mg APAP 650 mg Ibuprofcn 400 mg Placebo.	250 mean 23,9y 139F, 111M	Healthy subjects 16 years of age or older. Moderate or severe pain (score of at least 5 on VAS) as a result of an oral surgical procedure.	Single dose 8 hours	Completed; integrated, full	Severe pain not listed otherwise compatible with SmPC
Efficacy	TRAMAP·ANAG-10 CSR	Evaluation of the efficacy and safety of the combination tramadol 75 mg (TRAM) with acctaminophen (APAP) 650 mg in subjects experiencing pain from an oral surgical procedure and to demon-strate the contribution of each component to the analgesic effect of the combination	Randomized, double-blind, parallel-group, active-controlled factorial design trial with a placebo control.	(16 y - 46 y)	TRAM/APAP TRAM 75 mg APAP 650 mg Ibuprofcn 400 mg Placebo.	400 mean 21,5y 249F, 151M	Subjects ≥16 years of age and in otherwise good physical health were to have experienced moderate or severe pain (score of at least 5 on a visual analog scale) as a result of an oral surgical procedure involving extraction of two or more impacted third molars.	Single dose 8 hours	Completed; integrated, full	Severe pain not listed otherwise compatible with SmPC
Efficacy	TRAMAP·ANAG-03 CSR	Evaluation of the efficacy and safety of the combination tramadol 75 mg (TRAM) with acctaminophen (APAP) 650 mg in subjects experiencing pain from an oral surgical procedure and to demon-strate the contribution of each component to the analgesic effect of the combination	Randomized, double-blind, placebo-controlled, parallel-group, factorial design trial with an active control	(16 y - 33 y)	TRAM/APAP TRAM 75 mg APAP 650 mg Ibuprofcn 400 mg Placebo.	250 mean 18,8y 130F, 120M	Subjects ≥16 years of age and in otherwise good physical health were to have experienced moderate or severe pain as a result of an oral surgical procedure involving extraction of at least one impacted third molar.	Single dose 8 hours	Completed; integrated, full	Severe pain not listed otherwise compatible with SmPC

Assessor's comment:
Concerning these study reports no further evaluation has been performed due to the impossibility to separate out in this mixed population the users under 18 years.

Pfizer:

Tabular Summary of Sponsor Clinical Studies

Study Number	Code	Title	Investigator	Treatment Groups/# Pts	Age	Study Design	Study Indication	Study Status	Study Report Date	Summary of Results

Study Number	Code	Title	Investigator	Treatment Groups/# Pts	Age	Study Design	Study Indication	Study Status	Study Report Date	Summary of Results
n/a	<18;ibu	A Blinded, SingleDose, Parallel Study Comparing the Anitpyretic Efficacy and Safety of Ibuprofen Pediatric Suspension and Acetaminophen Suspension in Children with Fever	n/a	Ibuprofen pediatric suspension 7.5 mg/kg (78), acetaminophen suspension 10-15 mg/kg (82). Total n=160.	6 mo - 11 y/o	single-center, double-blind, balanced, parallel group, randomization stratified by baseline temp	fever reduction	completed	Jan-97	n/a
n/a	<18;ibu	A Comparative Evaluation of the Antipyretic Efficacy and Safety of Ibuprofen 50 mg Chewable Tablets and Ibuprofen 20 mg/mL Suspension in Children	Multicenter	Ibuprofen 50 mg chewable tablets (48), ibuprofen 20 mg/mL suspension (45). (amt dependent on weight). Total n=93.	2-11 y/o	randomized (stratified by baseline temp), single-blind, single-dose, parallel group, inhouse, multicenter	fever reduction	completed	Dec-97	n/a
n/a	<18;ibu	A Blinded, SingleDose, Parallel Study Comparing the Antipyretic Efficacy and Safety of Ibuprofen Pediatric Suspension and Acetaminophen Suspension in Children with Fever	n/a	Ibuprofen Pediatric Suspension 100mg/5mL (92), Acetaminophen Suspension 160mg/5mL (77). Total n=168.	6 mo - 11 y/o	Double-blind, randomized, parallel, stratified by baseline temperature, 8-hour follow-up	fever reduction	completed	Mar-99	n/a
AM-98-01	<18;ibu	Advil Liqui-Gel Migraine Headache Study I	Richard B. Lipton, MD: Innovative Medical Research, Inc., Stamford, CT	Advil (ibuprofen) Liqui-Gel 200 mg (198), Advil Liqui-Gel 400 mg (191), Advil Liqui-Gel 600 mg (198), Placebo (142). Total n=729.	12-64 y/o	Single-dose, randomized (stratified by gender and caffeine consumption), placebo-controlled, double-blind, parallel group, outpatient, multicenter	migrane heache pain	completed	Apr-99	Advil Liqui-Gels, at single doses of 200 mg, 400 mg, or 600 mg, relieved migraine headache. There was a slight trend favoring the two higher doses over the 200 mg dose. All three doses of ibuprofen were well tolerated.

Study Number	Code	Title	Investigator	Treatment Groups/# Pts	Age	Study Design	Study Indication	Study Status	Study Report Date	Summary of Results
n/a	<18;ibu	Advil Liqui-Gel Migraine Headache Study II	n/a	Advil 400 mg (2 x 200 mg + 1 placebo) (208), Advil 600 mg (3x 200 mg) (215), Placebo (3 x placebo) (164) (Liquigels). Total n=587.	12-72 y/o	Single-dose, randomized (stratified by gender and caffeine consumption), placebo-controlled, double-blind, parallel group, outpatient, multicenter	migrane heache pain	completed	Apr-99	n/a
PV-96-01	<18;ibu	Advil ® Liquigel Dental Pain Study I	Elliot Hersh, DMD, PhD: University of Pennsylvania, Philadelphia, PA	Advil ® liquigels 200mg (61), Advil ® liquigels 400mg (59), Extra Strength Tylenol 1000mg (63), Placebo (27). Total n=210.	16-42 y/o	Randomized (stratified by gender and baseline pain severity rating), placebo-controlled, single-dose, double-blind, double-dummy, parallel group, single center, inpatient	relief of pain following extraction of impacted third molar teeth	completed	Aug-98	Single 200mg and 400mg doses of a new Advil liquigel formulation provided faster times to relief for several onset measures and demonstrated overall superiority compared to Extra Strength Tylenol 1000mg and placebo.
PV-96-04	<18;ibu	Advil Liquigel Maximum Use Safety and Tolerance Study	Multicenter	Advil liquigel capsules (418), film-coated ibuprofen tablets (415), Advil liquigel placebo capsules, film-coated placebo tablets (413). Total n=1246.	12-83 y/o	multicenter, multiple-dose, double-blind, randomized (stratified according to age), parallel group	gastrointestinal adverse event profile	completed	Jun-97	The absence of any serious gastrointestinal adverse events and the low incidence of positive occult blood tests in this trial also support the safety of the liquigel formulation relative to the tablet and confirms the safety of OTC ibuprofen.

Study Number	Code	Title	Investigator	Treatment Groups/# Pts	Age	Study Design	Study Indication	Study Status	Study Report Date	Summary of Results
n/a	<18;ibu	Advil Liquigel Dental Pain Study II	n/a	Advil liquigel capsules 400mg, Extra Strength Tylenol caplets 1000mg, Placebo capsules/caplets. Total n=150.	16-43 y/o	Randomized (stratified by gender and baseline pain), placebo-controlled, single-dose, double-blind, double-dummy, parallel, single center, 6-hour evaluation period.	relief of pain following extraction of impacted third molar teeth	completed	Nov-98	n/a
n/a	<18;ibu	Advil Liquigel Headache Study II	n/a	2 Advil liquigel capsules (200mg) + 2 placebo caplets (100), 2 ES Tylenol caplets (500mg) (100) + 2 placebo liquigel capsules, 2 placebo caplets + 2 placebo liquigel capsules (53). Total n=253.	14-67 y/o	Single-dose, randomized (stratified by gender), placebo-controlled, double-blind, double-dummy, parallel group, single center (4-hour evaluation period)	relief of episodic tension-type headache.	completed	Oct-98	n/a
n/a	<18;ibu	Advil ® Liquigel Dental Pain Study III	n/a	Advil ® liquigels 200mg (60), Advil ® liquigels 400mg (62), Extra Strength Tylenol 1000mg (59), Placebo (31).Total n=212.	16-39 y/o	Randomized (stratified by gender and baseline pain severity rating), placebo-controlled, single-dose, double-blind, double-dummy, parallel group, single-center, inpatient	relief of pain following extraction of impacted third molar teeth	completed	Aug-98	n/a

Study Number	Code	Title	Investigator	Treatment Groups/# Pts	Age	Study Design	Study Indication	Study Status	Study Report Date	Summary of Results
n/a	<18;ibu	A Double-Blind, Single-Dose, Parallel Study Comparing Advil Liqui-Gel to Excedrin Extra-Strength / Excedrin Migraine and to Placebo in Migraine Headache	n/a	IBU liquigels 400 mg (2 x 200 mg capsules), acetaminoph en 500 mg + aspirin 500 mg + caffeine130 mg (2 x 250/250/65 mg caplets), placebo.	13-62 y/o	Double-blind, double-dummy single-dose, multicenter, parallel group, randomized (stratified by gender and caffeine consumption), placebo-controlled, out-patient study	relieving migraine headache	completed	Apr-00	n/a
n/a	<18;ibu	A Double-Blind, Single-Dose, Parallel Group Study Comparing Advil ® Liquigel To Extra Strength Excedrin/Excedrin Migraine, And To Placebo in Dental Pain	n/a	2 Advil liquigels 200 mg + 2 placebo caplets, 2 Excedrin caplets (acetamin. 500mg /aspirin 500mg /caffeine 130mg) + 2 placebo liquigels, 2 placebo liquigels + 2 placebo caplets.	16-50 y/o	Single-dose, randomized (stratified by gender and baseline pain severity), placebo-controlled, double blind, double-dummy, parallel group, single-center trial	relief of pain following extraction of impacted third molar teeth	completed	Feb-00	n/a

Study Number	Code	Title	Investigator	Treatment Groups/# Pts	Age	Study Design	Study Indication	Study Status	Study Report Date	Summary of Results
n/a	<18;ibu	Double-Blind, Placebo-Controlled, Maximum Use Safety and Tolerance Study of Advil® Liqui-Gel® andCelebrex™	Multicenter	Ibuprofen Advil Liqui-Gel, 1200mg/day for 10 days (908), Celebrex 200mg/day for 10 days (891), Placebo (450). Total n=2249.	12-92 y/o	Multi-center, randomized (stratified according to age), placebo-controlled, multiple-dose, double-blind, double-dummy, parallel group, outpatient	maximum use safety and tolerance	completed	Jul-01	n/a
PV-99-05	<18;ibu	A Double-Blind, Multiple Dose, Parallel-Group Study Comparing Advil ® Liqui-Gels ® to Celebrex™ and to Placebo in Dental Pain	James R. Fricke, Jr., DDS, MSD: PPD Pharmaco Inc., Dental Center, Austin TX	Advil (ibuprofen) Liqui-Gel 400 mg (3 doses) (74), Celebrex 200 mg (one dose) (74), and placebo (26). Total n=174.	16-45 y/o	Randomized (stratified by gender and baseline pain severity), placebo-controlled, multiple-dose, double blind, double-dummy, inpatient, parallel group, single-center	relief of dental pain following extraction of impacted third molar teeth	completed	Apr-00	Multiple 400-mg doses of Advil Liqui-Gels provided significantly faster relief from dental pain and demonstrated overall superiority to Celebrex (one 200-mg dose) and placebo during a 12-hour evaluation period. Celebrex provided significantly faster relief and superior overall analgesic efficacy compared to placebo.
n/a	<18;ibu	A Study Comparing the Efficacy of Two Ibuprofen Formulations	n/a	Single 400 mg dose (2 x 200 mg Advil liquigels, n=88), Equate ibuprofen softgels (2x200 mg, n=90) and placebo (n=33)	16-40 y/o	Randomized, stratified (by gender and baseline pain severity), placebo-controlled, in-patient, single-dose, double blind, parallel group, single-center study	relief of dental pain following extraction of impacted third molar teeth	complete, final report	Jul-09	n/a
n/a	<18;ibu	Ibuprofen 400 mg Effervescent Tablet	n/a	Ibuprofen effervescent	16-40 y/o	single-center, inpatient, single-	relief of dental pain following	complete, final	Sept-08	n/a

Study Number	Code	Title	Investigator	Treatment Groups/# Pts	Age	Study Design	Study Indication	Study Status	Study Report Date	Summary of Results
		Dental Pain Study II		tablet, 1 x 400 mg, dissolved in water (n=67), ASA/Vit C effervescent tablets (Aspirin® + Vitamin C), 2 x 400mg/240 mg, dissolved in water (n=72), IBU tablets (Nurofen®), 2 x 200 mg (n=72), placebo (n=37)		dose, randomized, placebo-controlled, doubleblind, parallel group trial.	extraction of impacted third molar teeth	report		
n/a	<18;ibu	A double-blind, single-dose comparison of ibuprofen vs. acetaminophen vs. placebo in the relief of post operative oral surgery pain	n/a	WM-295: ibuprofen 200 mg (n=32), acetaminophen 650 mg (n=28) placebo (n=34); WM-295A: ibuprofen 200 mg (n=27), acetaminophen 650 mg (n=27), placebo (n=27).	16-65 y/o	two-site, single-dose, double-blind, parallel, randomized, placebo-controlled	surgical removal of single boney impaction (dental pain)	complete, final report	Apr-87	n/a
n/a	<18;ibu	A double-blind, single-dose comparison of Advil (ibuprofen) vs. Tylenol plus codeine vs. placebo in the relief of post operative oral surgery pain	n/a	ibuprofen 400 mg (n=74), acetaminophen 600 mg/codeine 60 mg (n=75), placebo (n=79).	>=16	single-dose, double-blind, parallel, randomized, placebo-controlled	third molar extraction (dental) pain	complete, final report	Apr-87	n/a

Study Number	Code	Title	Investigator	Treatment Groups/# Pts	Age	Study Design	Study Indication	Study Status	Study Report Date	Summary of Results
n/a	<18;ibu	A double-blind, single-dose comparison of Advil 400 vs. APAP 1000 vs. placebo in the relief of post operative oral surgery pain	n/a	two Advil 200mg, APAP 1000mg, placebo. Total n=184	>=16	single-dose, double-blind, parallel, placebo	postoperative oral surgery (dental) pain	complete, final report	Apr-86	n/a
n/a	<18;ibu	A double-blind comparison of the safety and efficacy of a single dose of liquid formulations of ibuprofen (10mg/kg), acetaminophen 15mg/kg and a control vehicle in the relief of sore throat pain in children	n/a	ibuprofen 10mg/kg, (n=33), acetaminophen 15mg/kg (n=31), placebo (n=30)	2-12 y/o	single-dose, double-blind, randomized, parallel	sore throat pain	complete, final report	Jul-90	n/a
n/a	<18;ibu	Demonstration of the Analgesic Efficacy and Safety of Liquid Formulations of Ibuprofen (10mg/kg), Acetaminophen (15mg/kg), and Placebo in the relief of Orthodontic Pain in Children	n/a	Ibuprofen 10mg/kg, Acetaminophen 15mg/kg, Placebo	8-14 y/o	single-dose, double-blind	orthodontic pain	Complete, Final Report	Jun-95	n/a
n/a	<18;ibu	Double-blind, single-dose study of the safety and analgesic efficacy of ibuprofen liquid, acetaminophen liquid, and placebo (liquid vehicle) following orthodontic treatment	n/a	ibuprofen liquid, acetaminophen liquid, vehicle	8-14 y/o	single-dose, double-blind	orthodontic pain	complete, final report	Jun-95	n/a
n/a	<18;ibu	An open-label, actual use study of the safety of Children's Advil ibuprofen suspension 10mg/kg in children with various sources of discomfort requiring the use of an analgesic	n/a	Children's Advil suspension (203 children2-13 years of age)	2-12 y/o	open-label, multiple-dose, actual use	actual use	complete, final	Jun-88	n/a

Study Number	Code	Title	Investigator	Treatment Groups/# Pts	Age	Study Design	Study Indication	Study Status	Study Report Date	Summary of Results
n/a	<18;ibu	A double-blind study to demonstrate the safety and efficacy of a single dose of a liquid formulation of ibuprofen compared to a control vehicle in the relief of earache in children	n/a	ibuprofen suspension 10mg/kg, vehicle. Total n=93/120 children aged 5-12 years	5-12 y/o	single-dose, double-blind, parallel, randomized, placebo, 2-center	earache caused by otitis media (middle ear infection)	Complete final report	Oct-92	n/a

Assessor's comment:
Concerning these study reports please refer for evaluation to the preceding subsection 1 above.

Assessor's comment:
Overall conclusion concerning this section:
Pharmaceutical formulations used in the clinical studies related to ibuprofen in paediatric population only concern the oral formulations [oral suspension, tablet (chewable)].

Indications and posology
The submitted studies provide no new insights in the efficacy of ibuprofen in the symptomatic treatment of mild to moderate pain, and/or fever in children (from 6 months and above) and adolescents.

For the symptomatic treatment of mild to moderate pain, and/or fever the dosage of ibuprofen in children and adolescents depends on body weight and age respectively – in general with 7 to 10 mg/kg body weight as single dosage, up to a maximum of 30 mg/kg body weight as total daily dosage.

The MAHs stated that the submitted paediatric studies do not influence the benefit risk for ibuprofen and that there is no consequential regulatory action.

The MAHs submitted no clearly identified study data concerning children younger than 6 months. Regarding this no conclusions can be drawn in this context. Further, no study data were submitted with regard to pain and inflammation in rheumatic disease including juvenile idiopathic arthritis.

<u>Symptomatic treatment in fever:</u>
Symptomatic treatment of fever is a generally accepted indication for ibuprofen. The submitted studies provide no new insights in the efficacy of ibuprofen in fever treatment of children and adolescents

<u>Symptomatic treatment in mild to moderate pain:</u>
Symptomatic treatment of mild to moderate pain is a generally accepted indication wording for ibuprofen.

No conclusions can be drawn related to the following submitted pain studies:

• Johnson & Johnson:

- Protocols 90-002 &90-003: A comparison of the efficacy and safety of ibuprofen suspension dosed at 5 mg/kg and 10 mg/kg and acetaminophen elixir dosed at 12.5 mg/kg to placebo in children with ear pain.
- Protocols 89-949 &90-001: A comparison of the efficacy and safety of ibuprofen suspension dosed at 5 mg/kg and acetaminophen elixir dosed at 12.5 mg/kg to placebo in children with sore throat pain.
-> In these trials only single dose treatment was studied which has insufficient informative value.
- Protocol 90-048: A single dose study to compare the efficacy and side effects of ibuprofen suspension to placebo in children 5 through 11 years of age with post-operative pain secondary to either inguinal or umbilical herniorrhaphy.
-> The study was discontinued due to low/slow enrolment. No efficacy data are reported

V. ASSESSMENT OF RESPONSE TO QUESTIONS AND ASSESSMENT OF RECKITT BENCKISER'S SUBMISSION

V.1 Assessment of response to questions

Question 1 - DE. Concerning the non-oral formulations of ibuprofen the MAHs are requested to provide additional information about the respective marketing authorisations in the different EU countries.

Response Johnson & Johnson
The table below lists EU Member States' ibuprofen MAs for non-oral formulations, with strengths, indications and age groups.
English translations of the SmPCs are attached in Appendix1 of the response document.

COUNTRY	LOCAL TRADENAME	REGISTRATION NUMBER	GENERIC(S)	STRENGTH(S)	DOSAGE FORM	ROUTE(S) OF ADMIN	SmPC 4.1 Therapeutic Indication	Age
Germany	Dolormin Migräne Zäpfchen	13563.00.00	Ibuprofen	542.2mg	Suppository	Rectal	Acute treatment of headache in patients with migraine attacks with and without aura	Adults and adolescents of/over 15 years
Germany	Dolormin Mobil Gel	43767.00.00	Ibuprofen	5%	Gel	Topical	For sole or supportive external treatment in - swelling or inflammation of soft tissue around joints (e.g. bursae, tendons, tendon sheets, ligaments and articular capsule), - sports injuries and injuries due to accidents such as contusions, sprains, strains. Dolormin Mobil Gel is used by adolescents of/over 14 years and adults	Adolescents of/over 14 years and adults
Sweden	Ipren 125 mg suppository	15684	Ibuprofen	125mg	Suppository	Rectal	Short-term treatment of acute pain conditions of mild to moderate intensity and fever in patients with colds.	Adults, and children of/over 6 months and weighing more than 7 kg.
Sweden	Ipren 5% gel	18362	Ibuprofen	5%	Gel	Topical	For symptomatic treatment of local pain of mild to moderate intensity, due to muscle and joint injury, e.g. sporting injuries.	Adults and children from 16 years
Sweden	Ipren 60 mg suppository	46199	Ibuprofen	60mg	Suppository	Rectal	Short-term treatment of acute pain conditions of mild to moderate intensity and fever in patients with colds	Adults, and children of/over 6 months and weighing more than 7 kg

Response Pfizer
Details of the Marketing Authorisations (MAs) for non-oral formulations of ibuprofen, held by Pfizer Consumer Healthcare (PCH) throughout the EU, are provided in the Table below.

Country	Product name	Pharmaceutical form & strength	Indications	MA name	MA number
France	Advil Gel 5%	Gel, 5%	Symptomatic treatment: superficial tendinitis sprain, contusions	Pfizer Santé Familiale rue du Dr lannelongue 75014 Paris	100 g = 34009 360 944 0 6
France	Advil Gel 5%	Gel, 5%	Symptomatic treatment: sprain, contusions	Pfizer Santé Familiale rue du Dr lannelongue 75014 Paris	60 g = 34009 376 852 3 8

Response Reckitt Benckiser
Reckitt Benckiser has provided data on ibuprofen suppositories within the original submission for the Article 45 procedure which should now be with the BfArM for review. In addition, please see Appendix 1 of the response document for full details regarding the respective marketing authorisations across Europe for non-oral formulations (Ibuprofen 60/125 mg suppositories, Ibuprofen 5/10% Gel).

Assessor's comment:
Marketing authorisations for non-oral formulations of ibuprofen stated by the MAHs are ibuprofen 60/125 mg suppositories, ibuprofen 542.2 mg suppositories and ibuprofen 5%/10% gel.
Ibuprofen 60/125 mg suppositories are preponderantly indicated in the treatment of mild to moderate pain and/or fever. The abovementioned ibuprofen 542.2 mg suppositories by Johnson & Johnson are indicated in the acute treatment of headache in adolescents from 15 years with migraine attacks with or without aura.
Within this Article 45 procedure no study data concerning the ibuprofen formulation 5/20% gel were provided. Therefore, ibuprofen formulation gel is not further discussed.
Point resolved.

Question 2 - DE. Literature data are requested which give a comparison of the pharmacokinetic profile of ibuprofen between the paediatric population and adults.

Response Johnson & Johnson
The MAH has conducted a literature search in Medline and Embase to identify relevant published literature which was supplemented with additional papers identified from the MAH database.
The pharmacokinetics of ibuprofen are not affected by dose between 5 and 10 mg/kg or age ranges from 3 months and 10 years old. In febrile children, stereoselective pharmacokinetics had an appearance consistent with those previously demonstrated in adults [Davies 1998].
The differential pharmacokinetics of the individual enantiomers has been studied in children following a single oral dose of the racemate for post-operative analgesia [Rey 1994]. Plasma concentrations of the S-(+)-enantiomer were lower than those reported in adults, suggesting

a higher dosage might be required in infants. These differences may suggest impaired R-(–) to S-(+) inversion in the infant and/or a higher clearance of the S-(+) enantiomer. No relationship was evident for the S/R ratio and tmax suggesting a lack of pre-systemic gut inversion. In addition, lower urinary recovery of conjugated drug in infants (»3.5%) compared with adults (»9%) was evident. This difference has been attributed to either immature glucuronidation, a lower bioavailability, or to an increased formation clearance of ibuprofen to other metabolites. However, these differences did not reach statistical significance. The relative proportion of ibuprofen in synovial fluid in children seems to be slightly higher after repeated doses than in adults after a single dose. In adults, the Cmax of ibuprofen in synovial fluid is one-third of that in serum, whereas in children the Cmax in synovial fluid was about 40% of the maximal concentrations in serum [reviewed, Davies 1998].
Detailed reviews of age-related ibuprofen pharmacokinetics can be found in Davies [1998] and Rainsford [2009].

See references in Appendix 2 of the response document.

Response Pfizer
N/A

Response Reckitt Benckiser
Please refer to the expert report, pp. 10 to 26.

Assessor's comment:
Rainsford (2009) stated that with the exception of the conversion of R(-)-ibuprofen to its S(+) enantiomer the pharmacokinetic parameters of ibuprofen in children are comparable with those in adults and "it appears that the rate of conversion of R(-) ibuprofen is lower in children than it adults". Further, the brief account of Johnson & Johnson above is also referable.
Point resolved.

Question 3 - DE. The MAH Johnson & Johnson is asked to provide the bioavailability report of the paediatric study / Protocol No. 86-642.

Response Johnson & Johnson
The bioavailability report is attached Appendix 3 of the response document.

Assessor's comment:
The bioavailability report "Correlation of Antipyretic effect with Blood Levels of Ibuprofen in Febrile Children" / Protocol No. 86-642 has been provided.
Point resolved.

Question 4 - DE. The MAH Johnson & Johnson is asked to present the relevant PSUR documents which were described in the clinical overview.

Response Johnson & Johnson
The following PSURs are submitted separately due to their size:
- 1st January 2003 to 31st December 2009
- 1st January 2005 to 9th June 2010.

The remaining listed reports cover time periods within the above-mentioned PSURs so are not submitted.
- Addendum: 1st January 2008 to 31st August 2008
- Addendum: 1st January 2009 to 30th September 2009
- 1-year report 1st January 2009 to 31st December 2009

- 3-year report 1st November 2006 to 31st October 2009
- 3-year report 24th May 2005 to 23rd May 2008
- 5-year report 1st January 2003 to 31st December 2008.

Assessor's comment:
PSUR has been provided.
Point resolved.

Question 5 – DE. For text harmonisation reasons the MAH Pfizer is requested to propose the safety information for SmPC and PL concerning the new safety issue relating to hypovolemia and acute renal failure in paediatric patients.

Response Pfizer
PCH proposes SmPC and PL text relating to hypovolemia and acute renal failure, in the Table below.

Warning	Proposed SmPC (section 4.4) Text	Proposed Leaflet (section 2) Text
Hypovolemia	Use with caution in children under 12 years of age with hypovolemia or dehydration resulting from frequent vomiting, diarrhea, or insufficient ingestion of fluids. There have been reports of renal impairment in children with predisposing factors, such as fever, dehydration and the concomitant use of NSAIDs.	Use in children under 12 years old: Ask a physician before use if your child has not been drinking fluids or lost fluids due to continuous vomiting or diarrhoea.
Acute renal failure	Use with caution in children under 12 years of age with acute renal failure.	Use in children under 12 years old: Ask a physician before use if your child has kidney problems.

Assessor's comment:
Pfizer's proposed text is considered adjuvant. **Thus, the Rapporteur proposes the undermentioned safety information for the SmPC in section 4.4** in accordance with the approved SmPC of Nurofen/Nuroflex/Nurodon for Children 40 mg/ml oral suspension (procedure Nos.: DE/H/2204/001-002/DC, DE/H2206/001-002/DC, DE/H/2343/001-002/DC). Also in accordance with Rainsford, 2009, who mentioned that dehydration can play an important role in the occurrence of renal effects form all NSAIDs in view of their concentrating in the renal tubular system. The text is proposed also with reference to a retrospective study published by Misurac et al., 2013, who suggest that NSAIDs can lead to acute kidney injury in paediatric patients particularly those suffering from dehydration:

"Paediatric population
There is a risk of renal impairment in dehydrated children <*and adolescents*>."

Point resolved.

Question 6 – NL. For the sake of harmonization of the posology for children (≤ 12 years of age) it is proposed to advise a dosage based on kg bodyweight and not to determine a lower age limit for the treatment with ibuprofen, but instead a lower limit of bodyweight i.e. 5 kg, as the bodyweight is used as the primary criterion for the posology. The recommendation will remain 7 to 10 mg/kg body weight as single dosage, up to a maximum of 30 mg/kg body weight as total daily dosage.
This entails that the dosing table in section 4.2 of the SmPC should present an overview of bodyweight ranges and the corresponding single doses and corresponding total dose in 24 hours.

Response Johnson & Johnson
Johnson & Johnson supports the proposal from the Netherlands CMS to harmonise the posology for children (≤ 12 years of age) to a dosage recommendation based on body weight without a lower age limit but to include a lower limit of body weight of 5kg. The recommendation will remain 7 to 10 mg/kg body weight as single dosage, up to a maximum of 30 mg/kg body weight as total daily dosage.
Age-based dosing has been found to be imprecise and can result in inaccurate dosing due to marked variations in weight of children of the same age. Currently recommended dosage schemes often consist of wide age bands. As a result, children who are light for their age and receive the maximum recommended dose within the age band can receive a dose per kg bodyweight that differs from older, heavier children. Therefore the use of “age based” dosing guidelines may result in children being given more than the maximum recommended dose or less than the normal analgesic dose for their weight. For some children in pain, higher doses within the 7-10 mg/kg range may be required to provide adequate analgesia. From an efficacy perspective, weight-based dosing may be even more important than age-related dosing when treating pain compared with fever. Harmonisation to specific weight bands will therefore increase dose accuracy.
Parents and caregivers who understand that dosing should be based on weight rather than age or height of fever are less likely to give an incorrect dose.
Johnson & Johnson therefore supports the proposal to harmonise the posology for children (≤ 12 years of age) to a dosage recommendation based on body weight without a lower age limit but to include a lower limit of body weight of 5kg. For adolescents above the age of 12 the safety of dosing is of course still relevant, but small variations due to age related dosing are of less significance in this age group. We would therefore recommend retaining an age based dosing recommendation for simplicity.

Response Pfizer
PCH acknowledges the Agency’s proposals to i) introduce a 5 kg lower bodyweight limit (where relevant to a particular product) ii) include a dosing table in section 4.2 of SmPCs and iii) reference a bodyweight of ≥ 40 kg for the ≥ 12 year paediatric age group (referenced on page 9 of the day 89 draft assessment report).
PCH considers that the inclusion of bodyweight and age is helpful to support parents/carers of children to understand the appropriate dosage for the individual child. In some EU countries, parents would not necessarily be aware of their child’s weight at all times, furthermore a child’s weight can increase significantly over a short space of time. To overcome this issue and so as to ensure that parents/carers have sufficient information to administer the correct dose, PCH considers that an age range along with the corresponding bodyweight range, should be presented in the proposed dosing table. Furthermore, PCH considers that an advisory notice should accompany the table, stating that if known, bodyweight should always be used as the primary criterion for determining dosages; age should only be used if a child’s bodyweight is not known.

In summary, PCH agrees to the addition of the proposed dosing table to section 4.2 of the SmPCs of relevant EU MAs. However, it is recommended that the proposed table should include all of the changes highlighted above i.e. inclusion of both bodyweight and age ranges, a 5 kg minimum bodyweight and a ≥ 40 kg (≥ 12 year) category.
In terms of implementing the proposals into the product information of relevant PCH MAs, we will await the final recommendations and timescales published by the Agency following closure of the current Work Sharing Procedure.

Response Reckitt Benckiser
Reckitt Benckiser is in agreement with the evidence already reviewed under Article 45 and accepted by BfArM to support a posology for ibuprofen for infants from 5 kg in weight.

Age Range
Reckitt Benckiser would like to seek clarity on the suggested wording in the assessment report – "for use in children from 5 kg body weight (6 months)" as this is not aligned with the conclusion which states "not to determine a lower age limit for the treatment with ibuprofen".
Reckitt Benckiser propose that dosing instructions should include weight and the corresponding age (which may be market specific) to reflect current practices and ensure instructions are familiar and easy to implement.
The Draft PdAR references a recent procedure with the following wording as an example for section 4.2 of the SmPC - "for use in children from 5 kg body weight (6 months)".
We would like to draw attention to the differences that occur across Europe with regards to the ages correlating to 5kg. Data are presented in Appendix 2 of the response document which demonstrates that infants from the age of 3 months can have a 6kg median body weight. Therefore if 6 months is included as age guidance in relation to 5kg weight, this would not be in line with recognised growth charts or with what the consumer is accustomed to with currently approved products (see Appendix 8 of the response document). In many countries the product labelling may need to reflect both the minimum weight of 5kg along with the corresponding age bracket in accordance with local guidance. It should also be noted ibuprofen is commonly used for treatment of post-immunisation pyrexia from the age of 2 months and demonstrates a safety profile similar to paracetamol.
An assessment of available evidence on children's ibuprofen (see Appendix 2 of the response document), supports the recommendation to include age as well as body weight in dosing instructions. It is evident that, in many markets, dosing by age is standard practice and where dosing by kg bodyweight is not the accepted norm, confusion could arise leading to unsafe practices and increased pressure on primary healthcare services. In many countries access to a paediatrician or other healthcare provider is such that advice is readily available to enable parents to understand the most appropriate treatment and dosage for their child. However, analgesic medicines are often required when there is no such professional advice available and may involve the use of products which are already in the medicine cabinet at home. In these circumstances it is simpler for a parent to calculate the required dose based on the child's age, particularly in countries where weight is not generally used in the home for dosing children. This was highlighted in a recent study which showed that 40% of homes did not possess scales to accurately weigh their children.
Reckitt Benckiser as MAH therefore recommends that:
• Instructions should be provided on pack which will enable accurate dosing based on weight and the corresponding age (which may be market specific). This will ensure parents find instructions that are familiar and easy to implement and that accurate dosing is achievable in countries where weight-based dosing would create difficulties in the self-medication setting,
The following wording is proposed for the SmPC *"for use in children from 5kg body weight (insert corresponding age range)"*.

• It should also be acknowledged that ibuprofen is widely used for the treatment of post immunization pyrexia from the age of 2 months and demonstrates a safety profile similar to paracetamol which is used from birth in some countries.

Posology 7-10 mg/kg

Reckitt Benckiser proposes that the posology remains at 5-10mg/kg single dose with up to a maximum of 30mg/kg total daily dose, for oral ibuprofen formulations.
Evidence is presented to demonstrate that a posology of 5-10 mg/kg body weight delivers a dose of ibuprofen that is safe and effective in each age group including infants from the age of 2 months.
An appropriate posology of 5-10mg/kg body weight for ibuprofen in children, including age and weight segmentation (based on WHO weight for age tables), is included in Appendix 2 (table 2) of the response document. This posology has proven to be safe and effective in infants for many years and we believe that there is no benefit if this is changed as proposed. For example, Table 2 (Appendix 2) of the response document illustrates that a child in the 6m-1y age group weighing 10 kg would receive a single dose of 50mg of ibuprofen which equates to 5mg/kg. Therefore a dose range of 7-10mg/kg would increase the dose delivered to the child across currently approved products and cause confusion for parents. The 5-10mg/kg dose range is reflected in the posology of well-established ibuprofen children's products in addition to recently approved procedures (DE/H/3341/001-002/DC, referenced in the Draft PdAR). Although SmPC section 4.2 for procedure DE/H/3341/001-002/DC states that dosage is 7-10mg/kg body weight as a single dose, doses calculated from the SmPC dosing
table fall below this range for individuals at the upper boundary of weight ranges i.e. 9kg child (50mg ibuprofen; 5.6 mg/kg), 15kg child (100mg ibuprofen; 6.7mg/kg) and 29kg child (200mg ibuprofen; 6.9mg/kg).
Recently approved Reckitt Benckiser DCP procedures (DE/H/2204/001-002/DC, DE/H/2206/001-002/DC also reflect 5-10mg/kg dose range.
Therefore Reckitt Benckiser proposes that the posology remains at 5-10mg/kg single dose with up to a maximum of 30mg/kg total daily dose, for oral ibuprofen formulations.

Assessor's comment:
In accordance with Martindale (last modified 2010-09-10) "The Complete Drug Reference" in the UK oral doses of ibuprofen are given according to age recommended by the BNFC 20110/11 (http://bnfc.org/bnfc/) for the treatment of pain/fever. For Germany, national requirements – ordinance about the liability to prescription of medicinal products – refer to the age of children and therefore only stating the weight would not be suitable in this respect.

It can be stated generally that ibuprofen is not indicated in children < 5 kg body weight (corresponding to children below the age of 3 months and 6 months, respectively). In children below the age of 3 months no information concerning ibuprofen licences was submitted.
A dosing table including age range along with the corresponding body weight is recommendable.

However, the Rapporteur considers that the approved oral dose recommendations for ibuprofen products in children and adolescents are probably rather similar and should not be amended within this Article 45 procedure.

In view of the response of Reckitt Benckiser it can be stated that the change of an approved single dose recommendation of 5-10 mg/kg to 7-10mg/kg is considered not indicated within this procedure.

Conclusion: Harmonisation of the dose recommendations (to advise a dosage only based on kg body weight) appears not advisable within this Article 45 procedure due to the different regulatory requirements in the member states.

Point resolved.

VI.2 Assessment of Reckitt Benckiser's submission

The Rapporteur received the submission of Reckitt Benckiser after finalisation of the day 89 draft AR during the clock-stop phase.

Reckitt Benckiser remarked that many of the studies in the table below are old, and not reported to current standards.

Tabular summary of clinical studies (for further information please also refer to the response document trial_results_Nurofen_updated)

Protocol/ Study Report Number	Trial design	Interventions	Age	Number of subjects	Study Indication	Trial inter-ruption	Trial Report Date	Outcomes and estimation
1.) **BH0302**	This was a 2-part study. Part I was an open sensory evaluation of 16 analgesic suspensions by 8 adults. Part 2 was a single blind, randomised taste-testing study in healthy volunteers (153 adults and 153 children) to investigate acceptability of the organoleptic properties of 7 commercially available paediatric analgesic suspensions (3 ibuprofen and 4 paracetamol) and one ibuprofen test suspension. Participants tested 4 suspensions during visit 1 and 4 during visit 2.	On each of the two visits subjects received either 4 ibuprofen suspensions (1 mL of each, all 20 mg/mL) or 4 paracetamol suspensions (3 x 24 mg/mL and 1 x 50 mg/mL) orally. Samples were tasted and assessed one at a time. The total daily doses of analgesic actives taken by the consumers was: Paracetamol 122 mg (= 2.0 mg/kg for an average-weight adult and 7.4 mg/kg for an average-weight 4-year old child). Ibuprofen 80 mg (= 1.3 mg/kg for an average-weight adult and 4.8 mg/kg for an average-weight 4-year old child)	Children aged ≥ 4 and ≤ 7 years and healthy parents ≥ 18 years	153 adults, 153 children	taste testing	no	15. Sep 03	Nurofen for Children was preferred by significantly ($p<0.05$) more children than both Calprofen and Mandafen for Children (both ibuprofen suspensions). The taste of both Nurofen products (marketed and tested) was rated significantly ($p<0.05$) higher than both Calprofen and Mandafen for Children. Significantly ($p<0.05$) more adults preferred the test ibuprofen suspension to Nurofen for Children and both Calprofen and Mandafen for Children. Adults rated the taste of both Nurofen products significantly ($p<0.05$) higher than both Calprofen and Mandafen for Children. The taste of Calpol Infant (paracetamol) was rated significantly ($p<0.05$) higher than all other paediatric analgesic suspensions by both children and adults. This product was also particularly characterised by low levels of numbing and burning mouth feel attributes.

Protocol/ Study Report Number	Trial design	Interventions	Age	Number of subjects	Study Indication	Trial inter-ruption	Trial Report Date	Outcomes and estimation
2.) **BHI302 (Part I)**	A double-blind, parallel group, single-oral-dose, stratified, block-randomised study comparing the antipyretic properties of ibuprofen, acetaminophen and placebo in the treatment of pyrexia associated with infectious diseases in children.	Patients received a single oral dose on the basis of body weight of 1) ibuprofen 5 mg/kg, 2) ibuprofen 10 mg/kg, 3) acetaminophen 10 mg/kg or 4) placebo. Patients also consumed two placebo liquids to maintain the blind.	2 -11 y/o	A total of 127 patients were enrolled of which 9 were excluded from the efficacy analysis	pyrexia associated with infectious diseases	no	07. Aug 86	Results obtained for the total 118 valid patients, the total group of antibiotic free patients (n = 112), the low baseline temperature group (n = 66) and the subset of antibiotic free patients with the low baseline temperature group (n = 63) each showed that all active treatments were more efficacious than placebo ($p < 0.05$). There were no significant differences between active treatments in the low baseline temperature group and its non-antibiotic subset, but ibuprofen 10 mg/kg was more efficacious than acetaminophen ($p<0.05$) in the total valid patient group and the total antibiotic free group. In the high baseline temperature group (n = 52), both ibuprofen treatments were superior to placebo ($p<0.05$) and acetaminophen was superior to placebo for most assessments. In terms of AUC for percent temperature reduction over 4, 6 and 8 hours in this group, ibuprofen 10 mg/kg was superior to acetaminophen ($p<0.05$). Results were similar in the subset of nonantibiotic patients in the high baseline temperature group (n = 49) except that ibuprofen 10 mg/kg was superior to ibuprofen 5 mg/kg in terms of AUC in temperature reduction over 4, 6 and 8 hours ($p<0.05$). Hence a dose response for ibuprofen was shown in the high baseline temperature, antibiotic-free group of patients.
3.) **BPI 302 (Part II)** / Addendum to efficacy report	An open, parallel group, pharmacokinetic study in a subset of children to investigate the pharmacokinetics of ibuprofen and to determine whether the half life of ibuprofen is affected by age, dose and gender.	See above for BPI302 Part 1.	See above for BPI302 Part 1.	47 for PK analysis, of which 36 for Cmax, Tmax and AUC calculat. Of these 26 for elimination rate calculat..	PK study	no	16. Mai 88	The Cmax, Tmax and AUC data are not provided in the efficacy report or the addendum which considers determination of half-life. The mean half-life in the ibuprofen 10 mg/kg group was 1.58 hours (SD 0.316) and that in the ibuprofen 5 mg/kg group was 1.55 hours (SD 0.271). Overall, the mean half-life in children was 1.56 hours (SE 0.056; 95% CI 1.45 - 1.67) and that in adults (from a previous study) was 1.69 hours (SE 0.083; 1.51 - 1.87). The mean difference between adults and children was 0.13 hours (SE 0.100), the p value being 0.19.

Protocol/ Study Report Number	Trial design	Interventions	Age	Number of subjects	Study Indication	Trial inter-ruption	Trial Report Date	Outcomes and estimation
4.) **BP1320**	A multi-centre, open label, multiple dosage, study to determine the safety and tolerability of ibuprofen suspension in the treatment of mild to moderate pain of various etiologies in children.	Initial oral dose of 5 mg/kg followed, if necessary, by a second dose of 5 mg/kg within 2 hours. Doses of 5 or 10 mg/kg were given at 4-6 hour intervals i.e. at 4-6 hours and 8-12 hours after the initial administration. Thereafter, doses of 5 or 10 mg/kg were given as required up to a maximum of 40 mg/kg/day for up to 10 days.	6 mo -11 y/o	not given	treatment of mild to moderate pain of various etiologies	infor-mation not available	10. MAI 89	Information not available
5.) **BR1148 / CI195090**	An open study to investigate the use of ibuprofen suspension in the treatment of post-immunisation pyrexia in children.	Doses were calculated according to weight so that each child received a daily dose of 20 mg/kg ibuprofen divided into 4 doses. The calculated volume of ibuprofen suspension (20 mg/mL) was administered every 6 hours for 24 hours, then every 6 hours as needed up to 72 hours.	3 mo – 2 y/o	254 were recruited, of which 110 took medicat. Of these, 98 provided post-baseline data for the principal measures of efficacy	post-immunisation pyrexia	no	29. Nov 95	At 12 hours after the first dose, 50% of children had at least one rectal temperature less than 38 degrees C recorded. At endpoint, 68/93 (73%) showed an improvement in condition since the previous dose. At the time of the second dose, 60/91 (66%) subjects showed an improvement in their condition. At endpoint dose there was a mean improvement of 0.8 degrees C (95% CI: 0.6, 0.9) in rectal temperature compared with baseline. The factor for centre was not statistically significant. Seventy-five out of 98 (77%) subjects had a rectal temperature of less than 38 degrees C at the endpoint dose. The Kaplan-Meier estimate of first occurrence of a rectal temperature less than 38 degrees C was 11.9 hours. For 97/103 (94%) subjects, their parents considered the trial medication to have been either 'good' or 'very good'.

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6.) **M83064**	Parallel group design. Open label.	Patients admitted to the trial were given Ibuprofen 100 mg /5ml at a total dosage of either 20mg/kg or 30mg/kg daily, given in four divided doses at six hour intervals over a 24 hour period. Anti-infective agents were given were necessary, a record being made of the agent used, the dose, route of administration and the time of commencement. Aspirin and other non steroidal anti-inflammatory or analgesic agents were not allowed during the trial.	2 -12 y/o	50 patients entered the study. 6 patients were excluded due to protocol violations 23 receiving 20mg/kg and 21 receiving 30mg/kg completed the study.	fever reduction	no	04.10.1983	Both dosage levels caused highly significant reductions in temperature over baseline. The Fall in temperature was greater at the higher dosage level (5% level significance at the 12 and 20 hour measurements). In individuals receiving 20mg/kg ibuprofen, taste acceptability was good in 19 and very good in 4. With 30mg/kg ibuprofen, the corresponding groups were 18 and 3, the difference between the treatment groups being non-significant. No side effects were recorded for any of the patients in either treatment group and there were no withdrawals from the study.
7.) **M083079**	Open label, single dose, cross over.	Single dose of oral Ibuprofen syrup 7mg/kg body weight or crushed aspirin (oral) 15mg/kg body weight on consecutive days. The alternative treatment was given on the second day.	1 – 12 y/o	28 patients	fever reduction	no	24. Aug 83	The mean maximum fall in temperature was 2.02ºC with ibuprofen and 1.54ºC with aspirin. The differemce between the two drugs in terms of maximum dall was significant (P<0.05). Both ibuprofen and aspirin produced a significant fdall in mean initial temperature from 1 hour to 8 hours and throughout this period the mwan fall in temperature was greater with ibuprofen than aspirin, this difference, however, did not reach a level of statistical significance.
8.) **M83111 / M83080**	Open label, comparative, single dose.	Patients received in syrup form either ibuprofen (7 mg/kg body weight) or paracetamol (8 mg/kg of body weight) as a single dose	2 – 12 y/o	39 patients	fever reduction	no	30. Nov 83	Both ibuprofen and paracetamol produced significant reduction in the initial temperature from 1/2 hour to 8 hours of administration. No significant difference was found between the two drugs in terms of rate of reduction in temperature, degree or reduction in temperatuer and duration of reduction in trempérature.
9.) **M84058**	Single-blind parallel group study Investigating the antipyretic properties of ibuprofen syrup versus acetylsalicylic acid syrup in febrile children	A dose of either ibuprofen syrup (6mg/kg) or acetylic acid syrup (10mg/kg) was administered to the patient at baseline, if the body temperature at 1 hour was higher than baseline then the second dose was given. Some patients received antibiotics and some did not.	6 mo – 10 y/o	78 patients were randomized into the study 4 patients were excluded from the analyses	fever reduction	no	15 Mai 84	Although there were no significant differences between treatments at each timepoints, the absolute values of the Z-statistic at times 0.5 and 1 hour suggested that ibuprofen had an effect on temperature sooner than acetylsalicylic acid. Ibuprofen showing a greater reduction in temperature at times 0.5 and 1 hour (0.05<p<0.1). The differences between the antibiotic groups were not significant.

Protocol/ Study Report Number	Trial design	Interventions	Age	Number of subjects	Study Indication	Trial inter-ruption	Trial Report Date	Outcomes and estimation
10.) **M84148**	Comparative evaluation of antipyretic activity of ibuprofen and aspirin in children with pyrexia of varied aetiology	In each patient rectal temperature was recorded prior to and at 0.5, 1, 2, 3, 4, 5, 6 and 8 hours after administration of the trial drug. 2 readings were taken, the second one 5 mins after the first. The mean of the two readings were taken for analysis.	not given	28 patients studied, 16 were suffering from fever associated with URTI and 12 associated with other causes	fever reduction	no	11. Okt 84	Pyrexia due to URTI: with Ibuprofen Rf for the first 4 hours of drug administration was 0.5 and with Aspirin it was 0.33. Temperature fell to normal in 10 patients with ibuprofen and in 7 with aspirin. Results indicated a trend towards longer duration of effect with Ibuprofen. Pyrexia due to other causes: Ibuprofen and Aspirin produced a significant fall in the mean initial temperature from 1 hour to 8 hours of drug administration. Temperature fell to normal in eight patients with ibuprofen and aspirin. Ibuprofen and Aspirin were comparable in terms of Rf. Fmax. Df and Pn.
11.) **M84162 Part 1**	Open, comparative, randomised and parallel group study.	ibuprofen 20mg/kg/day in 3 divided doses and Paracetamol 30mg/kg/day in 3 or 4 divided doses	not given	not listed	soft tissue injuries	no	not available	not listed
12.) **M84162 Part 2**	Open, controlled, comparative and parallel group	ibuprofen 20mg/kg/day or aspirin 120mg/kg/day over 4 weeks	not given	not listed	rheumatic fever	no	not available	Good clinical response was observed in all patients treated with ibuprofen and all patients treated with aspirin. Three patients complained of epigastric pain of mild to moderate nature while on aspirin therapy, whilst no patients reported any side effects whilst on the ibuprofen treatment.
13.) **M85073** (internal)	Open label, comparative and between patients.	Single dose of ibuprofen 7mg/kg of body weight or paracetamol 8mg/kg body weight in a random order. Both were administered orally in syrup form. No other drug was received during the trial medication period.	2 – 12 y/o	39 children recruited. 26 with URTI and 13 from systemic viral infections.	fever reduction	no	28. Mai 85	UTRI group; Both ibuprofen and paracetamol produced significant reduction in the initial temperature from 0.5 hrs to 8 hrs. The initial mean temp of the paracetamol group was significantly higher so the data were analysed statistically using a test of analysis of covariance to adjust. With regards a comparison of rate of reduction in temp degree of reduction and duration of reduction the study showed comparable antipyretic activity. System viral infection group; both study drugs produced a significant reduction in initial temp from 0.5- 8 hrs. No significant difference was seen between the two treatments in terms of rate of reduction, degree of reduction and duration.

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14.) **M86010** (internal)	Two phase, open label, comparative and between patients. First phase assessed antipyretic activity of trial medication over 8 hours, second phase was a 5 day period where each patient continued on the randomised medication with the addition of antimicrobial therapy administered whenever required. Assessments everyday for 5 days.	Patients were given ibuprofen syrup 20mg/kg body weight (3 dose levels based on age) or paracetamol syrup (dose based on age 2-3 62.5 mg, 3-6 125 mg, 6-12 250 mg), (both orally). Dose were repeated 3x day. In the second phase, antimicrobial therapy administered whenever required	not given	45 children	fever reduction	no	03. Feb 86	UTRI Group: Both ibuprofen and paracetamol produced a significant fall in initial temperature from 0.5-8 hrs. Temperature fell to normal for all 13 patients with ibuprofen and 14 with paracetamol. Both treatments were comparable in terms of their antipyretic effect. Measles Group: Both treatments produced a significant fall in initial temperature from 0.5-8 hrs. Temperature fell to normal in 9 patients with ibuprofen and 8 in paracetamol. No significant difference was seen between the two treatment groups
15.) **M86054 (internal)**	Open label, comparative assessment of the antipyretic activity of Ibuprofen and paracetamol suspension in children	N/A	N/A	30 children	fever reduction	no	23. Apr 86	Due to non-compliance and protocol violations the data wasn't analysed
16.) **M86103 (internal)**	Single dose, double blind study comparing the efficacy and safety and dose response of ibuprofen, acetaminophen and placebo liquids.	Single dose of ibuprofen 5mg/kg (n=23) ibuprofen 10mg/kg (n=19), acetaminophen 10mg/kg (n=24) or placebo (n=24)	2 – 11 y/o	120 anticipated patients	fever reduction	no	20. Okt 86	Interim results of 90 patients showed that all active treatments were favoured over placebo in terms of fever control. At 4 and 6 hours, ibuprofen 10mg/kg was favoured over acetaminophen 10mg/kg. Ibuprofen 10mg.kg was especially effective for fevers >102.4degrees F providing greater temp control than acetaminophen 10mg.kg at 4, 6 and 8 hours. Ibuprofen plasma levels peaked prior to peak efficacy
17.) **M87017 / M87012** (internal)	A single dose, double blind study to compare the efficacy, safety and dose responses of ibuprofen (I) acetaminophen (A) and placebo (P) liquids	Ibuprofen 5 mg/kg (n=29) or 10mg/kg (n=25) or 10 mg/kg of acetaminophen (n=31) or placebo (n=33)	2 – 11 y/o	118 patients	fever reduction	no	16 Mrz 87	All active treatments were favoured over placebo (p<.05) and 10 mg / kg ibuprofen was favoured over acetaminophen 10 mg/ kg (p<.05) especially for fevers >39.2 degrees C. Ibuprofen plasma levels peaked 1-2 hours before minimal temp occurred but there was good agreement between I dose max fever reduction and both peak I levels and area under the curve calculation.

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18.) **M88095 / MS86534**	Double blind, parallel group, multiple dose, dose ranging study	Subjects were randomly allocated to receive one of four strengths of ibuprofen syrup: 2.5mg/ml, 5mg/ml, 10mg/ml or 20mg/ml according to body weight. 4 study medications were identical in outward appearance and similar in taste. A supplementary (rescue) medication as provided at 2.5mg/kg (10mg/ml) was permitted. Antibiotics and other concomitant therapy were permitted during the study but always recorded.	overall mean age 2.6 y	100 children were recruited between February 1987 and May I988.	dose ranging study in fever reduction	yes	23. Dez 88	The trial was stopped 60 patients short of the planned entry because it had already exceeded the one year recruitment period stated in the protocol. The minimum effective dose of ibuprofen according to the pre-set study criteria •of• a l°C or more, reduction in body temperature at three hours is 5.0 mg ibuprofen/kg body weight. Age had no effect on this finding in a study in which most children (82%) were under four years. old.
19.) **M88126**	Open, dose response, controlled, not randomized	Children were started on dose regimen of 10 mg/kg/day ibuprofen syrup (as 3 doses: after breakfast, after school and at bedtime) at the first visit. Subsequent visits were at least every 4 weeks, the dose being increased by 10 mg/kg/day up to a maximum of 40 mg/kg/day or until a satisfactory response was obtained. Note: 1 child was started on 35 mg/kg/day due to disease severity and 1 on 25 mg/kg/day due to a flare in systemic symptoms.	18 mo – 13 y/o	44 children	efficacy and safety study in juvenile chronic arthritis	no	17. Aug 89	The dose providing an adequate response was 10 mg/kg (1 child), 15 mg/kg (3), 20 mg/kg (12), 25 mg/kg (1), 30 mg/kg (12), 35 mg/kg (3) and 40 mg/kg (5). There was no significant difference between mean joint count at the end of 1 month of treatment (mean 7.0) compared with baseline (mean 9.5). At the end of 2 months, there was a significant reduction in number of active joints (mean 4.8, $p = 0.02$). The same reduction was apparent after 3 months treatment. A significant reduction in disease severity was apparent compared with baseline (mean 4.9) at months 1, 2 and 3 (mean 3.7, 2.8 and 2.6, respectively, $p \leq 0.0002$ for all) as well as when comparing months 1 and 2 ($p = 0.0025$) and months 1 and 3 ($p = 0.0005$). Twelve children required concomitant medication. Several children had slight abnormalities in some biochemical parameters but these were considered common in JCA disease states. Long term follow-up: 17 children continued on ibuprofen syrup, 4 changed to ibuprofen tablets, 7 lost to follow-up, 8 in remission and 2 required change to other medication becasue of little benefit.

Protocol/ Study Report Number	Trial design	Interventions	Age	Number of subjects	Study Indication	Trial inter-ruption	Trial Report Date	Outcomes and estimation
20.) **M89062**	An open, parallel group study to compare the efficacy of ibuprofen syrup with that of paracetamol syrup.	Patients received either ibuprofen syrup (Brufen, 20 mg/kg daily in 3 divided doses) or paracetamol syrup (10-15 mg/kg three times daily). Study drugs were administered for 4 - 15 days according to individual patients need.	3 – 13 y/o	56 children	efficacy study in soft tissue injuries	no	03. Aug 89	Statistically significant improvement was seen in each parameter of assessment on Day 4 compared with pre-treatment for both treatments ($p<0.01$ for all).There was significantly greater reduction in severity of pain and tenderness with ibuprofen than with paracetamol on Day 4 ($p<0.01$ for both parameters). For swelling, the pre-treatment mean score had been significantly higher in the paracetamol group than the ibuprofen group pre-treatment and a further analysis was undertaken for swelling, taking the baseline values into account. Significantly more patients showed greater reduction of swelling of severe degree with ibuprofen than with paracetamol on Day 4 ($p<0.01$). There was no significant treatment difference in terms of restriction of movement. Significantly fewer days were required for complete recovery in the ibuprofen group (6.8 days, SEM 0.37) than in the paracetamol group (9.8 days, SEM 0.58) ($p<0.01$).

Protocol/ Study Report Number	Trial design	Interventions	Age	Number of subjects	Study Indication	Trial inter-ruption	Trial Report Date	Outcomes and estimation
21.) **M90077 / M87515**	A double-blind, randomised, parallel group, multiple dose study of the antipyretic activity and tolerability of ibuprofen and paracetamol in burn pyrexia in children.	Children received either ibuprofen (30 mg/kg/24 hours) or paracetamol (40 mg/kg/24 hours) 6-hourly for up to 14 days. Children weighing 7.0 - 20.9 kg received either ibuprofen syrup (15 mg/mL) or paracetamol syrup (20 mg/mL). Children weighing 21.0 - 60.0 kg received either ibuprofen syrup (45 mg/mL) or paracetamol syrup (60 mg/mL).	6 mo – 12 y/o	99 children entered the study (48 ibuprofen, 51 para-cetamol) 25 (10 ibuprofen, 15 para-cetamol) withdrew due to lack of response	temperature reduction in burn pyrexia	no	14. Nov 91	Reduction in temperature at 4 hours was significant for both treatments (p<0.001), with a mean temperature of 37.9 and 38.0 degrees C for the ibuprofen and paracetamol groups, respectively. The mean temperature reduction was 0.83 and 0.77 degrees C in the ibuprofen and paracetamol groups, respectively, with corresponding confidence intervals of 0.53 to 1.13 and 0.59 to 0.96 degrees C. The differences between treatment groups were not significant. There were also no significant differences between treatment groups for the analysis of temperature during the first 6 hours of study. At 3 hours, no patient was reported to have a worsening condition and for 14/43 children (33%) in the ibuprofen group and 12/49 (24%) children in the paracetamol group, the clinical condition had improved. The temperature remained below 37.5 degrees C for 2 consecutive doses for 35/43 (81%) children in the ibuprofen group and 35/47 (74%) in the paracetamol group. A greater proportion of children in the ibuprofen group had an improved clinical condition 3 hours after dosing.
22.) **MA91006**	Randomized, blinded, single dose study comparing the antipyretic efficacy of IBU suspension and APAP elixir.	IBU suspension at 5 mg/kg or 10 mg/kg and APAP elixir at 10-15 mg/kg	6 mo – 8 y/o	There were 60 patients assigned to the IBU group and 60 assigned to the APAP group.	fever reduction	no	02.02.1994	IBU reduces a child's fever faster than APAP when used according to labelling. the higher dose of temperatures greater than 102.5F is verified as an appropriate dosing regimen in cases of more severe febrile state (defined as temperature > 102.5"F) IBU exhibits further superiority over AP AP. six hours following dosing, the mean temperature of patients remained lowered and was more then 2°F lower than the mean temperature of the AP AP group. The mean temperature of the APAP group had risen to within one degree of the baseline fever.

Protocol/ Study Report Number	Trial design	Interventions	Age	Number of subjects	Study Indication	Trial inter-ruption	Trial Report Date	Outcomes and estimation
23.) **MACR86007 / BPI302**	A double-blind, parallel-group, stratified, block-randomized, single-dose study design was used in this eight-hour comparative trial.	buprofen 5 mg/kg Ibuprofen 10 mg/kg Acetaminophen 10 mg/kg	not given	127 children enrolled, 118 children evaluable for efficacy analysis	pyrexia associated with infectious diseases	no	07. Aug 86	Ibuprofen 10 mg/kg was found to be significantly more effective ($p < 0.05$) than acetaminophen 10 mg/kg with respect to maximum percent reduction of temperature and area under the percent reduction time curves through 4, 6, and 8 hours when analyzed in the total evaluable patient group, the total antibiotic-free group, the high baseline temperature group, and the subset of nonantibiotic patients in the high baseline temperature group. However, ibuprofen 5 mg/kg was not significantly different from acetaminophen 10 mg/kg
24.) **NL0116**	An open, randomised, comparative, parallel group study to compare the efficacy of Nurofen for Children suspension with that of paracetamol suspension in children with acute respiratory viral illness.	Children received either Nurofen for Children (10 mL [200 mg ibuprofen] for those aged 7 - 9 years and 15 mL [300 mg ibuprofen] aged 10 - 12 years) or paracetamol suspension (10 mL [240 mg paracetamol] for those aged 7 - 9 years and 20 mL [480 mg paracetamol]) for those aged 10 - 12 years, 3 times per day (every 8 hours). Treatment was taken for 2 days.	7 - 12 y/o	30 received Nurofen for Children and 30 received Paediatric Panadol. Efficacy and safety data from all 60 children were described.	pyrexia with acute respiratory viral illness	no	16. Aug 02	On Day 1, in the Nurofen group the onset of action (time for temperature to become normal) was within 1 hour for 15 patients and within 2 hours for 15 patients, and in the Panadol group the onset was within 1 hour for 18 patients and within 2 hours for 12 patients. On Day 2, onset of action in the Nurofen group was within 30 minutes for 3 patients, 1 hour for 24 patients and 2 hours for 3 patients and in the Panadol group onset was within 1 hour for 26 patients and 2 hours for 4 patients. The duration of the effect on Day 1 in the Nurofen group was 2, 4 and 6 hours for 1, 14 and 15 patients, respectively, and in the Panadol group it was 2, 4, 6 hours for 10, 16 and 4 patients respectively. The equivalent figures for Day 2 for the Nurofen group were 2, 4, 6 and 8 hours for 1, 5, 20 and 3 patients and in the Panadol group were 4 and 6 hours for 16 and 14 patients, respectively. These data were not analysed statistically.
25.) **NL0409** Study has been published but PMID is not known	A multi-centre, double blind, double dummy, parallel group, prospective, randomised study to compare the efficacy of a single dose of 10 mg/kg ibuprofen with 15 mg/kg paracetamol followed by tolerability over up to three days of open label dosing.	Patients were randomised to either Ibuprofen oral suspension administered at 10 mg/kg plus paracetamol placebo or to paracetamol oral suspension administered at 15 mg/kg plus ibuprofen placebo. Patients received a single dose followed by up to 3 days of open label dosing.	3 mo – 12 y/o	303 were randomized of which 9 withdrew. 301 were included in the ITT population.	fever reduction	no	26 Jul 06	The ITT analysis of the primary endpoint showed that there was no statistically significant difference between the treatments. The mean AUC0-6 for ibuprofen was -7.77 (SD 3.54) and for paracetamol was -7.66 (SD 3.76), the mean difference (ibuprofen - paracetamol) being -0.09, 95% CI -0.89, 0.71, $p = 0.82$.

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26.) **UF87010 / BPI310**	A double blind, multicenter, multiple dose, parallel group study comparing the efficacy of three dose levels of ibuprofen versus acetaminophen.	Ibuprofen suspension administered every 6 hours (q.6.h.) in doses of 2.5 mg/kg, 5 mg/kg, and 10 mg/kg in comparison with acetaminophen elixir 15 mg/kg q.6.h. in the 48 hour	Not available	Only 6 children were enrolled in 12 months	fever reduction and finding of the optimum dose levels	yes	16 Mai 89	Information not available. Poor patient recruitment. There were too few patients to make any judgments regarding efficacy, though at least some temperature reduction was seen for each patient.

Assessor's comment:
The stated pharmaceutical formulations used in the clinical studies related to ibuprofen in the paediatric population concern the oral formulations [suspension, liquids, syrup].

Study indications:
- 1 taste study [table above *No. 1.)* BH0302]
- 1 PK study [*No. 3.)* BPI 302 Part II]
- 14 studies in fever [(*No. 6.)* M83064, *No. 7.)* M083079, *No. 8.)* M83111 / M83080, *No. 9.)* M84058, *No. 10.)* M84148, *No. 13.)* M85073, *No. 14.)* M86010, *No. 15.)* M86054, *No. 16.)* M86103, *No. 17.)* M87017 / M87012, *No. 18.)* M88095 / MS86534, *No. 22.)* MA91006, *No. 25.)* NL0409, *No. 26.)* UF87010 / BPI310]
- 1 study in mild to moderate pain [*No. 4.)* BP1320]
- study in pyrexia associated with infectious diseases [*No. 2.)* BHI302 Part I, *No. 23.)* MACR86007 / BPI302]
- 1 study in pyrexia with acute respiratory viral illness [*No. 24.)* NL0116]
- 1 study in post-immunisation pyrexia [*No. 5.)* BR1148 /CI195090]
- 2 studies in soft tissue injuries [*No. 11.)* M84162 Part 1, *No. 20.)* M89062]
- 1 study in rheumatic fever [*No. 12.)* M84162 Part 2]
- 1 study in juvenile chronic arthritis [*No. 19.)* M88126]
- 1 study in burn pyrexia [*No. 21.)* M90077 / M87515]

Submitted data are considered not sufficient to give any recommendations for ibuprofen within this procedure in the treatment of:
- pyrexia associated with infectious diseases (BHI302; Part I, MACR86007 / BPI302: presented information not sufficient, too little study population)
- pyrexia with acute respiratory viral illness (NL0116: open-label study)
- post-immunisation pyrexia (BR1148 /CI195090: open-label study)
- soft tissue injuries (M84162 Part 1 and M89062: open-label studies)
- rheumatic fever (M84162 Part 2: open-label study)
- juvenile chronic arthritis (M88126: open-label study, not randomized)
- burn pyrexia (M90077 / M87515: in ibuprofen group nearly 21% showed lack of response)

Safety: The MAH's given table do not show any unexpected adverse reactions.

Conclusion: Data do not result in any new recommendations for the paediatric population.

Further 22 clinical studies in the paediatric population (1 month – 16 years) were listed in the response document, Appendix 6:
• 11 studies in juvenile pyrexia (BR0115, BR9083, NL0113, M86002 (M88132), M90013, M89065, SD7016, M89144, M84021, BR0105, BR9095)
• 3 studies in juvenile pyrexia and pain (BR0118, BR1151, MS92002)
• 2 studies in juvenile chronic arthritis (M86088, M83104), 1 study in juvenile rheumatoid arthtritis (BPI301)
• 2 studies in post-operative pain (BR9074, BPI304)
• 1 study in juvenile pain, inflammation and/or fever (MS83/29)
• 1 study in teething pain (BR1147)
• 1 study in pyrexia associated with infectious diseases (M83081)

Assessor's comment:

Pharmaceutical formulations used in the clinical studies related to ibuprofen in paediatric population concern the oral formulations primarily oral suspension/syrup. Only one study NL0113 (open label, non-comparative) investigated ibuprofen 60/125 mg suppositories in juvenile pyrexia, see Appendix 6 of the response document. 3 studies investigated juvenile chronic arthritis (M88126: open, dose response, controlled, not randomized study; M86088: open label, dose range response study; M83104: open labelled, uncontrolled study) and 1 study investigated juvenile rheumatoid arthritis (BPI301: double blind, parallel, comparative, randomised study without placebo control). However, given data are considered not sufficient to recommend ibuprofen for the treatment of juvenile idiopathic arthritis within the scope of this Article 45 procedure. The same applies to the study indications juvenile inflammation, teething pain and pyrexia associated with infectious diseases. In view of study BPI301 it should be noted that non-inferiority trials to an active reference with known efficacy but without a placebo arm are not recommended in accordance with Guideline on Clinical Investigation of Medicinal Products for the Treatment of Juvenile Idiopathic Arthritis (CPMP/EWP/422/04). Also in study BR9074 (pain relief following tonsillectomy) the placebo arm is missing in accordance with Guideline on the Clinical Development of Medicinal Products Intended for the Treatment of Pain (EMA/CHMP/970057/2011).

Convincing study data (double-blinded, placebo-controlled) for children younger than 3 months with details of the minimum weight were not provided (BR0115, M86002 (M88132), MS92002, M86088, M84021). In addition, in children below the age of 3 months no information concerning ibuprofen licences was submitted.

Reckitt Benckiser responded to the following points raised by the draft preliminary paediatric assessment report:

SmPC section 4.1
The assessment report only considers the indications of mild to moderate pain/fever for ibuprofen.

Response
Reckitt Benckiser agree that ‘symptomatic treatment of mild to moderate pain’ is a generally accepted indication wording for ibuprofen, however we would recommend that the broad range of indications currently approved for ibuprofen products across Europe are maintained. Subsets of indications such as post immunisation pyrexia, fast and effective relief of the symptoms of colds and influenza and mild to moderate pain, sore throat, teething pain, toothache, earache, headache, backache, minor aches and sprains, muscle pain, period pain, are included in section 4.1 of the SmPC for a significant number of ibuprofen products across Europe (see Appendix 8).
Although it is not stated explicitly in the Draft PdAR that changes to current indication wording is being sought by the Rapporteur, in the context of OTC use in children it is important that specific pain/fever examples such as these are included in the indication wording in the SmPC and Patient Information Leaflet to enable parents & carers to understand the situations in which the use of the medicine is appropriate. Self-medication often requires the use of a product already in the medicine cabinet at home and which may have been purchased for another type of pain or fever. It is therefore essential that indication wording includes specific pain/fever examples on pack/PIL which are meaningful to parents and carers.
It is also noted that the German document, BfArM Mustertext 8000198 Ibuprofen / Ibuprofen-DL-lysinat (apothekenpflichtig) spcde-ibuprofen-div-otc-2013-05-07-013, itself allows specific indications in the context of mild to moderate pain i.e.

4.1 Indications

Symptomatic treatment of:
- Mild to moderate pain
- Fever
[Optionally the first bullet point can be amended for clarification:
like headache, dental pain, menstrual pain.
This enumeration is conclusive. Other areas of use have to be substantiated by case].
A report is provided which demonstrates that parents rely on specific indications to select the appropriate medicine and administer it correctly and safely to their child. The report presents the available scientific evidence on the efficacy and safety of ibuprofen for treating various self limiting acute ailments/conditions in children less than 18 years of age (please refer to Appendix 7).

Reckitt Benckiser as MAH strongly recommends that, where SmPCs and Patient Information in Member States include specific indications within the context of mild to moderate pain and fever, these should be maintained.

SmPC section 4.2
Duration of treatment
The Rapporteur proposes the following updates for SmPC, section 4.2 and PL, section 3:
For OTC use of oral ibuprofen formulations in the symptomatic treatment of mild to moderate pain and/or fever
- in children (age range: ≥ 6 months to < 12 years):
"If [in children] this product is required for more than 3 days, or if symptoms worsen a doctor should be consulted."
- in adolescents (age range: ≥ 12 years to < 18 years):
"If <in adolescents [and adults]> this product is required for more than 3 days in case of fever or for more than 4 days for the treatment of pain, or if the symptoms worsen a doctor should be consulted."

Response
The MAH has paediatric ibuprofen products for the specified OTC indications, for short-term use only. Duration of treatment varies depending on product, age of the child and market (see Appendix 3) but in some cases, for older children, is up to 10 days.
Reckitt Benckiser as MAH agrees with the BfArM (as proposed in Draft PdAR) that an appropriate duration of treatment (before consulting the doctor) would be 3 days for children ≥6m-<12y (pain and fever), and 3 days (fever) or 4 days (pain) for adolescents ≥12y-<18years.
Reckitt Benckiser further recommends that even shorter duration of treatment prior to consulting the doctor is appropriate for the youngest age group, namely:
For OTC use of oral ibuprofen formulations :
- for younger infants, less than six months, professional medical advice should be sought if symptoms persist after 24 hours:
"For children under 6 months medical advice should be sought after 24 hours use (3 doses) if the symptoms persist."
- for post immunisation pyrexia a doctor be consulted if fever is not reduced after 2 doses:
"One 2.5ml dose followed by one further 2.5ml dose 6 hours later if necessary. No more than two 2.5ml doses in 24 hours. If the fever is not reduced, consult your doctor"
Please see Appendix 7.

Assessor's comment:
SmPC, section 4.1

Whereas 'symptomatic treatment of mild to moderate pain' is a generally accepted indication wording for ibuprofen, a broad range of indications are currently approved for ibuprofen products across Europe. Since the Article 45 procedure is not expected to be a full harmonisation process no recommendation with regard to Section 4.1 is given. On the other side submitted data do not result in any (new) indication recommendations for the paediatric population. Given data in Appendix 7 concerning 'post immunisation pyrexia', 'symptomatic relief of influenza', 'symptomatic relief of sore throat' and 'pain associated with otitis media' are considered not sufficient to implement this indication wording through this Article 45 procedure.

Certainly, the indication wordings '**short-term symptomatic treatment of fever and pain in the common cold'** in children from 20 kg body weight (6 years old) (e.g. procedure no. DE/H/1482/001) and 'symptomatic treatment of acute migraine headaches with or without aura' in children from 6 years and from 20 kg body weight have been accepted in several MS already.

But furthermore, conclusive study data concerning the **migraine headache indication** are not given in the MAHs' submission for this Article 45 procedure.

SmPC, Section 4.2

Post immunisation pyrexia is a non-approved indication in many MS including DE. Due to submitted data no further conclusions can be drawn about this indication. The abovementioned corresponding safety information concerning post immunisation pyrexia is considered not relevant given the here discussed indications mild to moderate pain and/or fever. Furthermore, see the proposed wording recommendations below concerning infants (age range: ≥ 3 months to ≤ 5 months) weighing more than 5 kg.

The Rapporteur proposes following additional wording for OTC use in the symptomatic treatment of mild to moderate pain and/or fever due to harmonisation reasons:

Oral medicinal products

• where applicable, in infants (age range: ≥ 3 months to ≤ 5 months) weighing more than 5 kg:

"For infants aged 3 - 5 months medical advice should be sought if symptoms worsen or not later than 24 hours if symptoms persist."

• in children (age range: ≥ 6 months to < *(≤)* 12 years):

"If <in children <aged from 6 months>> this product is required for more than 3 days, or if symptoms worsen a doctor should be consulted."

Remark: If in the dose recommendation the 12-years-old adolescent represents the eldest user group, the Rapporteur recommends that for the 12-years-old adolescent the abovementioned recommendation is also applicable for consistency reasons.

• in adolescents (age range: ≥ 12 years to < 18 years):

"If <in adolescents <and adults>> this product is required for more than 3 days in case of fever or for more than 4 days for the treatment of pain, or if the symptoms worsen a doctor should be consulted."

- where migraine [headache] is an approved supplementary indication:

"If <in adolescents <and adults>> this product is required for more than 3 days in case of migraine <headache> or fever, or for more than 4 days for the treatment of pain, or if the symptoms worsen a doctor should be consulted."

OTC use of suppositories in the symptomatic treatment of mild to moderate pain and/or fever:

• where applicable, in children (age range: ≥ 3 months to ≤ 5 months)

"For children aged 3 - 5 months medical advice should be sought if symptoms worsen or not later than 24 hours if symptoms persist."

• in children (age range: ≥ 6 months to < (≤) 12 years):

"If <in children <aged from 6 months>> this product is required for 3 days, or if symptoms worsen a doctor should be consulted."

• in adolescents (age range: ≥ 12 years to < 18 years) –

"If <in adolescents <and adults>> this product is required for more than 3 days in case of fever or for more than 4 days for the treatment of pain, or if the symptoms worsen a doctor should be consulted."

Remark: The information above is not applicable in migraine [headache] indication.

CMS' comments on Day 90 Finalised pdAR:

HU agrees with the overall conclusion and recommendation of the Rapporteur and has no further comments.

UK: The MHRA agrees with the overall conclusion of the Rapporteur. However, the MHRA has some additional points for consideration by the Rapporteur and other MS before adopting final recommendations for the SmPC.

1. It is not within the remit of this Paediatric Work Sharing procedure under Article 45 to propose any change to the adult SmPC wording. The proposed change in the adult wording for Ibuprofen oral and suppository preparations *"If <in adolescents <**and adults**>> this product is required for more than 3 days in case of fever or for more than 4 days for the treatment of pain, or if the symptoms worsen a doctor should be consulted."* is therefore not acceptable.
2. There is no evidence to support the advice that adolescents who are using Ibuprofen for pain should wait an additional day before seeking medical advice. Furthermore segmenting the ages and indications will cause confusion among patients and carers. In the interests of clarity on this matter, the wording should be *"If in children aged from 6 months to < 18 years this product is required for more than 3 days, or if symptoms worsen, a doctor should be consulted."* for both oral and suppository preparations.
3. We endorse the Rapporteur's conclusion that harmonisation of the dose recommendations across the EU (i.e. to advise a dosage only based on kg body weight) is not possible through the data submitted as part of this Article 45 procedure.

Assessor's comment:

The UK comments have been taken into account. Please refer to the recommendation in section VI. below.
Point resolved.

NL: The Netherlands agrees with the overall conclusions of the Rapporteur.

Unfortunately our request for an adaptation of the lower age limit (3 months instead of 6 months) by an additional inclusion of a lower bodyweight limit (i.e. 5 kg) has been interpreted as a request for stating the bodyweight only. This was, however, not our intention. Although it is preferred to use the bodyweight as indication for the posology in clinical practice, we agree with the combined specification of age and bodyweight as long as both the lower age limit of 3 months and a lower limit of the bodyweight of 5 kg are applied.
The maximum single dose of 10mg/kg bodyweight up to a maximum of 30 mg/kg bodyweight as total daily dosage is agreed.

Due to the misunderstanding the Rapporteur's conclusion is not clear. We agree with the Rapporteur that the harmonisation of the dose recommendations (to advise a dosage only based on kg body weight) is not necessary, but a combination of age and weight ranges is requested. As this combination of ranges has been already implemented in NL for the posology of ibuprofen in children, adaptation of the SmPC's in NL is not required.

Assessor's comment:
Harmonisation of the dose recommendation has not been implemented within this Article 45 procedure. However, it can be stated that ibuprofen is not indicated in the symptomatic treatment of mild to moderate pain and/or fever in children < 5 kg body weight (corresponding to children below the age of 3 months and 6 months, respectively). We agree, that dose recommendations including age range along with the corresponding body weight is favoured.
Point resolved.

<u>Outstanding point raised by the MAH Reckitt Benckiser:</u>

SmPC, Section 4.2

Reckitt Benckiser would like to confirm that post immunisation pyrexia is an approved indication, included in section 4.1 of the SmPC for ibuprofen products in a number of member states including Bulgaria, Croatia, Czech, Hungary, Latvia, Malta, Poland, Romania, Slovak and the UK (please see Appendix 3 of previous submission).

Reckitt Benckiser considers the data submitted to be relevant to post immunisation pyrexia which is an example of mild to moderate fever, an indication discussed within the report.

Several studies submitted with our original response clearly demonstrate Ibuprofen as a valuable and effective treatment for mild to moderate pyrexia due to infectious illness in children. Reckitt Benckiser believes this indication can be extended to cover treatment of post-immunisation pyrexia as the etiology of pyrexia resulting from the introduction of antigens either artificially via vaccination, or naturally via transfer of infective pathogens is identical. Both causalities stimulate the same immune-responsive cascade of pyrogenic agents which affect the temperature regulatory activity of the hypothalamus and result in an increase in body temperature, which above the norm of about 37 degrees can be considered to be a state of pyrexia. Ibuprofen inhibits the production of prostaglandins, which are some of the pyrogens released in the immune response, and also acts through modulation of the hypothalamus 'thermostat' to restore normal body temperature through an as yet unknown mechanism. Post-

immunisation pyrexia can cause significant distress for the child and care-giver due to increased crying, fretfulness, anorexia and drowsiness of the patient and therefore there is a great benefit for a rapid and effective treatment to reduce the patient's body temperature. Fever with most vaccines begins within 24 hours and lasts up to two days so it is an indication that falls under the appropriate time frame of use for OTC ibuprofen. Therefore Reckitt Benckiser believes there is sufficient relevant evidence to support the indication of post-immunisation pyrexia for Nurofen for Children in the OTC market.

In line with the existing approved indication for post immunisation pyrexia, many ibuprofen licences contain the following additional wording in section 4.2 of the SmPC:
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 2.5ml doses in 24 hours. If the fever is not reduced, consult your doctor.
Reckitt Benckiser believe that this wording should be included by the Rapporteur as part of the proposed additional wording for OTC use in the symptomatic treatment of mild to moderate pain and/or fever for the purpose of harmonisation.

Assessor's comment:
In fact, Reckitt Benckiser submitted only one study in post-immunisation pyrexia [No.5.) BR1148 /CI195090], p. 58 above, which was an open-label, non-randomised study. Due to the submitted data no further conclusions can be drawn about this indication. Therefore, no respective wording for post-immunisation pyrexia is recommended within this procedure for the SmPC in section 4.2 and section 4.1, respectively.
Point resolved.

VI. FINAL RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Overall conclusion
No special new aspects regarding the indication 'symptomatic treatment of mild to moderate pain and/or fever' and the dosing of ibuprofen in the named indication were detected.
Only a few updates relating to the safety information and the treatment duration are considered indicated. The text as recommended below should be selected or deleted as appropriate.

Recommendation
The appropriate variation to be requested from the MAH within 60 days to introduce the following wording for the paediatric population in the SmPCs and PLs:

<u>Oral medicinal products and suppositories</u>:

SmPC, section 4.4 and PL, section 2 'Warnings and precautions':

"There is a risk of renal impairment in dehydrated <children> <and> <adolescents>."

<u>OTC use of oral medicinal products in the symptomatic treatment of mild to moderate pain and/or fever</u>:

SmPC, section 4.2 and PL, section 3:

• where applicable, in infants (age range: ≥ 3 months to ≤ 5 months) weighing more than 5 kg:

"For infants aged 3 - 5 months medical advice should be sought if symptoms worsen or not later than 24 hours if symptoms persist."

• in children (age range: ≥ 6 months to < 12 years) and/or in adolescents (age range: ≥ 12 years to < 18 years):

"If <in children <aged from 6 months>> <and> <in adolescents > this medicinal product is required for more than 3 days, or if symptoms worsen a doctor should be consulted."

OTC use of suppositories in the symptomatic treatment of mild to moderate pain and/or fever:

SmPC, section 4.2 and PL, section 3:

• where applicable, in children (age range: ≥ 3 months to ≤ 5 months):

"For children aged 3 - 5 months medical advice should be sought if symptoms worsen or not later than 24 hours if symptoms persist."

• in children (age range: ≥ 6 months to < 12 years) and/or in adolescents (age range: ≥ 12 years to < 18 years):

"If <in children <aged from 6 months>> <and> <in adolescents > this medicinal product is required for 3 days, or if symptoms worsen a doctor should be consulted."

Request for supplementary information
Not applicable

VII. LIST OF MEDICINCAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

For Johnson & Johnson:

Country	**Medicinal Product**
Belgium	Perdofemina 400 mg filmomhulde tabletten
	Perdophen pediatrie 2% suspensie voor oraal gebruik
	Perviam 400 mg Filmcoated Tablets
	Perviam 200 mg filmomhulde tabletten
Germany	Dolormin Migräne Filmtabletten
	Dolormin extra
	Dolormin extra (Dolormin 400 mg)
	Tispol IBU-DD
	Dolormin Schmerztabletten
	Dolormin Schmerztabletten (Dolocalm)
	Ibu 342 Lysinat JJ
	Dolormin für Kinder Ibuprofensaft 2 %
	Dolormin Migräne Zäpfchen
	Dolormin für Kinder Ibuprofensaft 4 %
	Dolormin Migräne schnell lösliches Granulat

Country	Medicinal Product
	Dolormin compact bei Erkältungsschmerzen und Fieber
	Dolormin instant schnell lösliches Granulat
Ireland	Provin 100mg/5ml Oral Suspension
Italy	ANTALFORT 400 mg compresse rivestite con film
	ACTIGRIP FEBBRE E DOLORE 200 mg compresse rivestite con film
	ANTALGIL 200 mg compresse
Luxembourg	Perdofemina 400 mg comprimés pelliculés
	Perviam 400 mg compimés pelliculé
	Perviam 200mg comprimés pelliculés
Portugal	Perdofen 400 mg Coated tablets
Spain	Doctril 400 Forte
	DOCTRIL 200
Sweden	Ipren 200 mg filmdragerad tablett
	Ipren 400 mg filmdragerad tablett
	Ipren 20 mg/ml oral suspension
	Ipren 5% gel
	Ipren 125 mg suppositorier
United Kingdom	Ibuprofen 100 mg / 5 ml Oral Suspension
	Calprofen 100mg/5ml Oral Suspension Ibuprofen
	Ibuprofen oral suspension 100mg/5ml
	Ibuprofen oral suspension 100mg/5ml

For Pfizer:

Country	Medicinal Product Name	Dosage Form	Strength
Belgium	Advil 400 mg	Effervescent tablet	400 mg
	Advil-Mono Liquid Caps 200	Soft capsules	200 mg
	Advil-Mono Liquid Caps 400	Soft capsules	400 mg
	Advil-Mono 200	Tablet	200 mg
	Advil-Mono 400	Tablet	400 mg
Czech Republic	ADVIL EFFERVESCENT 400 MG	Effervescent tablet	400 mg
	Advil RAPID	Soft capsule	400mg
France	ADVILEFF 200 mg	Effervescent tablet	200 mg
	ADVILEFF 400 mg	Effervescent tablet	400 mg
	AdvilCaps 200	Soft capsule	200 mg
	AdvilCaps 400	Soft capsule	400 mg
	Advil Enfants et Nourrissons	Suspension	20 mg/ml
	Advil 100 mg Coated Tablet	Tablet	100 mg
	AdvilTab 200	Tablet	200 mg
	Advil 200 mg Coated Tablet	Tablet	200 mg
	AdvilTab 400	Tablet	400 mg
	Advil 400 mg Coated Tablet	Tablet	400 mg
	Advil 5% Gel	Topical gel	5%w/w
Germany	Spalt Ibuprofen 200 mg	Effervescent tablet	200 mg
	Spalt Ibuprofen forte 400 mg	Effervescent tablet	400 mg
	Spalt Kopfschmerz	Soft capsule	200 mg
	Spalt Forte	Soft capsule	400 mg
	Spalt Migraine	Soft capsule	400 mg

Country	Medicinal Product Name	Dosage Form	Strength
	Spalt Mobil	Soft capsule	400 mg
Greece	Advil	Soft capsule	200 mg
	Advil	Soft capsule	400 mg
	Advil	Suspension	20 mg/ml
	Advil	Tablet	200 mg
	Advil	Tablet	400 mg
Hungary	Advil 400 mg	Effervescent tablet	400 mg
	Advil Ultra	Soft capsules	200mg
	Advil Ultra Forte	Soft capsules	400mg
Ireland	Advil 200mg	Effervescent tablet	200 mg
	Advil Maximum Strength 400 mg	Effervescent tablet	400 mg
	Advil Liquigel 200 mg	Soft capsule	200 mg
	Seclodin 400 mg	Soft capsule	400 mg
	Seclodin 400 mg	Tablet	400 mg
Italy	Advil Effervescente 200 mg	Effervescent tablet	200 mg
	ADVILDOL 200 mg	Effervescent tablet	200 mg
	Advil Effervescente 400 mg	Effervescent tablet	400 mg
	ADVILDOL 400 mg	Effervescent tablet	400 mg
	Advil Istant Liquigels	Soft capsule	200 mg
Luxembourg	Advil-Mono Liquid Caps 200	Soft capsules	200 mg
Malta	Anadin LiquiFast 200 mg	Soft capsule	200 mg
	Anadin LiquiFast 400 mg	Soft capsule	400 mg
Netherlands	Advil bruis met citrussmaak, 400 mg	Effervescent tablet	400 mg
	Advil Liquid-Caps 200	Soft capsule	200 mg
	Advil liquid-Caps 400	Soft capsule	400 mg
	Advil Ovaal 400	Tablet	400 mg
Portugal	Anadvil EFE 200 mg	Effervescent tablet	200 mg
	Anadvil EFE 400 mg	Effervescent tablet	400 mg
Romania	Advil Ultra	Soft capsule	200mg
	Advil	Tablet	200mg
Slovak Republic	Advil 400mg	Effervescent tablet	400 mg
	Advil FORTE	Soft capsule	400mg
Spain	Ibuprofeno Wyeth 400 mg	Effervescent tablet	400 mg
United Kingdom	Advil 200mg	Effervescent tablet	200 mg
	Anadin LiquiFast 200 mg	Effervescent tablet	200 mg
	Advil 400 mg	Effervescent tablet	400 mg
	Anadin LiquiFast 400 mg	Effervescent tablet	400 mg
	Advil Liquigel 200 mg	Soft capsule	200 mg
	Anadin Ultra 200 mg / Anadin LiquiFast 200 mg	Soft capsule	200 mg
	Advil Liquigel 400 mg	Soft capsule	400 mg
	Anadin Ultra Double Strength 400 mg / Anadin LiquiFast 400 mg	Soft capsule	400 mg
	Anadin Ibuprofen 200 mg	Tablet	200 mg
	Anadin Joint Pain	Tablet	200 mg
	Advil 400 mg Tablets	Tablet	400 mg

For Reckitt Benckiser:

Medicinal Product
Ibuprofen 60mg Suppositories
Ibuprofen 125mg Suppositories
Ibuprofen 100mg Meltlets Strawberry
Ibuprofen 200mg Meltlets Lemon
Ibuprofen 200mg Meltlets Mint
Ibuprofen 2% Orange Suspension
Ibuprofen 2% Orange Syrup
Ibuprofen 2% Strawberry Suspension
Ibuprofen 4% Orange
Ibuprofen 4% Strawberry
Ibuprofen 200mg Capsule
Ibuprofen 400mg Capsules
Ibuprofen Lysine 200mg Caplets
Ibuprofen Lysine 200mg Tablets
Ibuprofen Lysine 400mg Powder
Ibuprofen Lysine 400mg Caplets
Ibuprofen Sodium 256mg Tablets
Ibuprofen Sodium 256mg Effervescent Tablets
Ibuprofen Sodium 512mg Tablets
Ibuprofen 200mg Caplets
Ibuprofen 200mg Tablets
Ibuprofen 400mg Tablets
Ibuprofen 200mg Effervescent Microgranules
Ibuprofen 400mg Effervescent Microgranules
Ibuprofen 300mg Hard SR Capsules
Ibuprofen 5% Gel
Ibuprofen 10% Gel