2. SYNOPSIS

Name of Sponsor/Company McNeil Consumer Products Company ***Name of Finished Product:*** ***Name of Active Ingredient:*** ibuprofen	***Individual Study Table Referring to Part of the Dossier*** ***Volume:*** ***Page:***	(For National Authority Use Only)

Title of Study: Efficacy and pharmacokinetic/pharmacodynamic profile of ibuprofen chewable tablets versus ibuprofen suspension in febrile children. CSR 167S. Protocol 91-113, Unpublished Report 293A and Unpublished Report 1475.

Investigators:

Study Centers:

Publication (reference):

Study Period: ***Phase of Development:***

Date of first enrollment:

Date of last completed:

Objective:

Methodology: Randomized, Open-label, Multicenter, Parallel

Children with low fever (101-102.5°F orally, or 102-103.5°F rectally) received IBU 5 mg/kg. Children with high fever (> 102.5-104.5°F orally, or > 103.5-105.5°F rectally) received IBU 10 mg/kg.

Number of Subjects (planned and analyzed): 71 subjects were included in the efficacy analysis and 83 subjects were included in the safety analysis. In the ibuprofen 5 mg/kg tablet group, 18 subjects were included in the efficacy analysis and 20 subjects in the safety analysis. In the ibuprofen 5 mg/kg suspension group, 16 subjects were included in the efficacy analysis and 19 subjects in the safety analysis. In the ibuprofen 10 mg/kg tablet group, 18 subjects were included in the efficacy analysis and 22 subjects in the safety analysis. In the ibuprofen 10 mg/kg suspension group, 19 subjects were included in the efficacy analysis and 22 subjects in the safety analysis.

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Diagnosis and Main Criteria for Inclusion: 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.

Test Product, Dose and Mode of Administration, Batch Number:

- Ibuprofen 5 mg/kg, tablet (chewable) oral
- Ibuprofen 5 mg/kg, suspension oral
- Ibuprofen 10 mg/kg, tablet (chewable) oral
- Ibuprofen 10 mg/kg, suspension oral

Duration of Treatment: This was a single-dose study.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Criteria for Evaluation:

Efficacy:

Safety:

Statistical Methods:

SUMMARY - CONCLUSIONS

Efficacy Results: In the ibuprofen 5 mg/kg tablet group, there were 11 females and 9 males. In the ibuprofen 5 mg/kg suspension group, there were 9 females and 10 males. In the ibuprofen 10 mg/kg tablet group, there were 14 females and 8 males. In the ibuprofen 10 mg/kg suspension group, there were 6 females and 16 males.

TEMPDIFF (temperature difference from baseline) (least squares mean): At 7h, 10 mg/kg tablets – 1.60, 10 mg/kg susp 2.63, p=0.005; at 8h: 10 mg/kg tablets 1.39, 10 mg/kg susp 2.11, p=0.05. 8 h SUMDIFF (sum of differences from baseline in temperature) (least squares mean): 5 mg/kg tablets – 13.86, 5 mg/kg susp – 15.09, p=NS, 10 mg/kg tablets –

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18.87, 10 mg/kg susp – 21.78, p=NS. MAXDIFF (maximum difference from baseline in temperature) (least squares mean): 5 mg/kg tablets - 3.00, 5 mg/kg susp - 2.98, p=NS, 10 mg/kg tablets - 4.02, 10 mg/kg susp - 3.90, p=NS. Mean total time of temperature reduction of ≥ 1°F (h): 5 mg/kg tablets – 5.94, 5 mg/kg susp - 6.39, p=NS, 10 mg/kg tablets – 5.61, 10 mg/kg susp - 6.85, p=0.023. Mean number of hours of an improved clinical response (h): 5 mg/kg tablets - 1.87, 5 mg/kg susp – 1.99, p=NS, 10 mg/kg tablets – 1.98, 10 mg/kg susp - 2.37, p=NS. Mean global evaluation (5-point categorical scale): 5 mg/kg tablets - 2.74, 5 mg/kg susp - 3.00, p=NS, 10 mg/kg tablets - 2.57, 10 mg/kg susp - 2.87, p=NS. Number of subjects using rescue medication: 5 mg/kg tablets - 8, 5 mg/kg susp - 3, 10 mg/kg tablets - 7.

Safety Results: AEs reported in more than 1 subject: tablet- urinary tract infection (2), viral illness/syndrome (3). There were no AEs related to study drug. One subject was hospitalized for shigallosis. One subject who vomited the study medication was discontinued, and 1 subject discontinued due to an adverse reaction to amoxicillin.

PK Results: Mean Vd/F (apparent volume of distribution per fraction of drug absorbed, L/kg): low fever (5 mg/kg tablet-0.247, 5 mg/kg susp-0.177), high fever (10 mg/kg tablet-0.205, 10 mg/kg susp-0.174). Mean k_a (first order rate constant for drug absorption, 1/h): low fever (5 mg/kg tablet-1.782, 5 mg/kg susp-5.441), high fever (10 mg/kg tablet-2.496, 10 mg/kg susp-4.182). Mean β (1/h): low fever (5 mg/kg tablet-0.148, 5 mg/kg susp-0.363), high fever (10 mg/kg tablet-0.189, 10 mg/kg susp-0.360). Mean K_{el} (first order rate constant for drug elimination, 1/h): low fever (5 mg/kg tablet-0.459, 5 mg/kg susp-0.488), high fever (10 mg/kg tablet-0.483, 10 mg/kg susp-0.497). Mean K_{eo} (first order rate constant for drug loss from effect site, 1/h): low fever (5 mg/kg tablet-0.813, 5 mg/kg susp-0.739), high fever (10 mg/kg tablet-0.830, 10 mg/kg susp-0.383). Mean EC_{50} (drug concentration producing 50% of maximum effect, µg/mL): low fever (5 mg/kg tablet-10.507, 5 mg/kg susp-7.370), high fever (10 mg/kg tablet-12.662, 10 mg/kg susp-8.254). Mean gamma (sigmoidicity factor of sigmoid Emax and inhibition functions): low fever (5 mg/kg tablet-2.086, 5 mg/kg susp-2.888), high fever (10 mg/kg tablet-2.214, 10 mg/kg susp-2.393). Mean t_{lag} (absorption lag time, h): low fever (5 mg/kg tablet-0.16, 5 mg/kg

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susp-0.14), high fever (10 mg/kg tablet-0.20, 10 mg/kg susp-0.13).

Conclusions: Conclusions were not provided in the clinical study report.

Date of the Report: April 1994