SYNOPSIS

Name of Company: Pharmacia AB **Name of Finished Product:** Ipren® suppositories 125 and 60 mg **Name of Active Ingredient:** Ibuprofen	*(For National Authority Use only)*
Open Label Pharmacokinetic Study of a Single Dose Ibuprofen Suppository in Children with Fever	
Protocol Number: 573-CHC-9127-001	**IND Number:** None
Investigators: Bengt W Granström, MD (center 1), Mikael Stenlund, MD (center 2)	
Study Centers: 1) Dept. of Pediatrics, University Hospital of Lund, Lund, Sweden 2) Dept. of Pediatrics, Hospital of Skellefteå, Skellefteå, Sweden	
Publication Reference: None as of the date of this report.	
Studied Period (Years): 06 June 2001 – 09 April 2003	**Phase of Development:** 2

Objectives:

Primary:

- To describe the pharmacokinetics of a single dose ibuprofen suppository in children.

Secondary:

- To describe the antipyretic effect of a single dose ibuprofen suppository in children.
- To examine if the pharmacokinetics of ibuprofen suppository was age dependent.

Methodology:
This was an open label, single dose, phase II study in children over 6 months old, with fever and presence of venous access performed in two Swedish study centers.

No other antipyretics were allowed from four hours before and until four hours after administration of study medication. If necessary, paracetamol (Panodil®) suppositories could be used as rescue drug.

The patients received one dose of ibuprofen suppository according to body weight, 5-10 mg/kg. Clinical laboratory screening tests were performed in connection with the pre-study health examination. Body temperature and blood samples for determination of ibuprofen plasma concentrations were taken immediately before the administration and then at 6 time points during 8 hours after the administration. Safety and tolerability were evaluated by spontaneous adverse event reporting during the 8 hours study period.

The following pharmacokinetic parameters were determined: AUC_{∞}, CL/F, C_{max}, t_{max}, Vd/F.

Number of Patients (Planned and Analyzed):
18 planned and 18/19 analyzed (PK and PD/Safety)

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Diagnosis and Main Criteria for Inclusion:
Children with fever and venous access, over 6 months old, body weight 7-50 kg, body temperature over 38.5°C.

Test Products, Dose and Mode of Administration, Batch Numbers:

Name: Ibuprofen suppository **Pkg Lot:** BK 2-1	**Strength:** 60 mg **Mfg:** Oct 2000	**Dose:** 5-10 mg/kg **Exp:** Oct 2003	**Route:** Rectal
Name: Ibuprofen suppository **Pkg Lot:** BE 5-1	**Strength:** 125 mg **Mfg:** May 2000	**Dose:** 5-10 mg/kg **Exp:** May 2005	**Route:** Rectal
Name: Ibuprofen suppository **Pkg Lot:** CK2	**Strength:** 60 mg	**Dose:** 5-10 mg/kg **Exp:** Oct 2004	**Route:** Rectal
Name: Ibuprofen suppository **Pkg Lot:** CL6	**Strength:** 125 mg	**Dose:** 5-10 mg/kg **Exp:** Nov 2006	**Route:** Rectal

Duration of Treatment:
All treatments were given as single-doses.

Criteria for Evaluation:

Pharmacokinetics:
Patients with at least one plasma sample taken after administration were included in the evaluation.

Pharmacodynamics:
Fever over 38.5°C.

Safety:
Start of administration of the study medication.

Statistical Methods:

Descriptive statistics showing median, mean, SD, min and max for continuous variables were tabulated for pharmacokinetic variables, body temperature, and demographic variables.

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SUMMARY OF RESULTS AND CONCLUSIONS:

Disposition of Patients and Baseline Characteristics:
Nine females and 10 males with fever (≥38.5°C) and venous access were included in this study. One male patient (No.25) was excluded from the pharmacokinetic and pharmacodynamic evaluation because of loose stools after administration and a body weight over 50 kg. Thus, 18 patients were included in the pharmacokinetic and pharmacodynamic evaluation. The patients were 0.6-15.3 (mean 6.2) years old, weighing 7.6-49.3 (mean 23.0) kg, and with an initial body temperature of 38.5-40.5 (mean 39.4)°C.

Pharmacokinetic Results:
The average maximum plasma concentration of ibuprofen, 23.3 mg/L, was reached 0.3-2.1 (mean 1.3) hours after the administration. C_{max} and AUC_{∞} increased slightly with increasing doses per body weight respectively per BSA. C_{max} appeared to occur earlier with lower body weights, i.e. in younger children. The average AUC_{∞} measured 57, 122 and 90 h×mg/L and the average clearance/F measured 0.114, 0.058 and 0.081 L/h/kg for the doses 60, 125 and 250 mg, respectively. The AUC_{∞} appeared to be lower and the clearance/F higher for the youngest children.

Pharmacodynamic Results:
The maximum observed decrease of body temperature was about 2°C (range 0.6-3.5) for all dose groups and was observed after 2-8 (mean 3.9) hours. The effect on temperature was higher in the oldest children as compared to the youngest children (E_{max} of 2.5°C *vs* E_{max} of 2.0 and 1.8°C).

Safety Results:
The treatment was well tolerated. Three adverse events were reported during the trial, all non-serious, moderate and judged not to be related to the study medication. No patient discontinued treatment due to adverse events.

CONCLUSIONS:

The youngest children appeared to have a slightly higher clearance/F and earlier t_{max} as compared to the older children.

The maximum decrease of body temperature appeared to be largest in the oldest children.

The treatment was clinically safe.

Date of the Report:	**Study Report Document Number:**
05 December 2003	573-CHC-9127-001-SR1