CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-944

MEDICAL REVIEW

MEDICAL OFFICER REVIEW

NDA 20,944
Sponsor: Whitehall-Robins Healthcare
Agent: Advil Chewable
Bioequivalence study
Date: February 24, 1998, revised July 16, 1998
Reviewer: Kent Johnson, MD

Introduction:

The sponsor has supplied data to support its assertion that their 50mg and 100mg Advil Chewable Tablet formulations are equivalent in antipyresis to the marketed ibuprofen suspension.

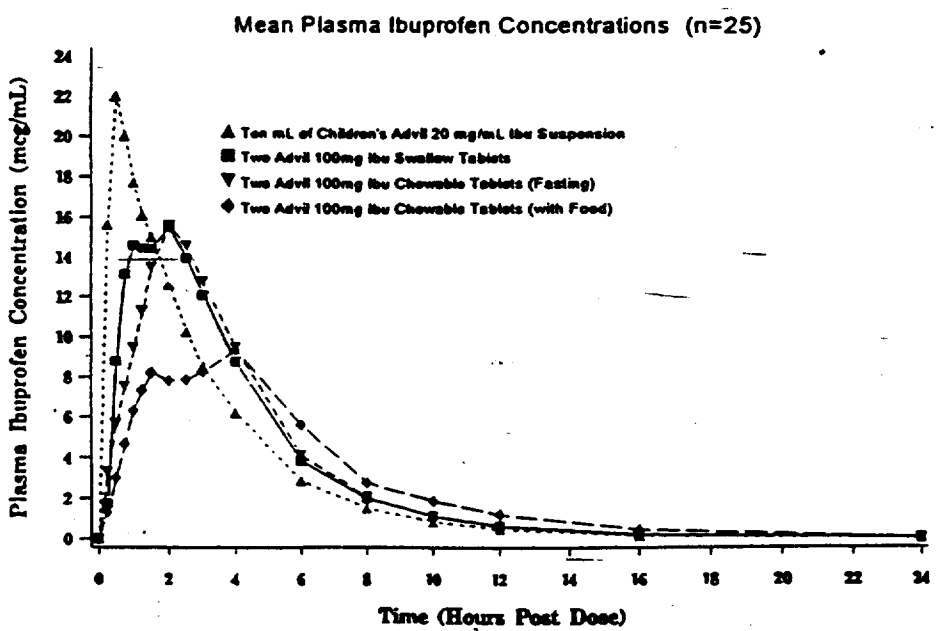
Pharmacokinetic study (protocol AF-95-03)

Design: This was a single-dose, four-way crossover, randomized study in 25 healthy males and females, comparing the bioavailability of 200mg dose of Advil chewable under either fasted or fed conditions with Children's Advil suspension 20mg/ml and Advil 100mg swallowable tablets, both given under fasted conditions.

Results: The values for Tmax, T1/2, AUCinf,and Cmax are given below:

	Tmax	T1/2	AUC	Cmax
suspension - fasted	0.6	2.1	68.7	22.9
swallow tabs - fasted	1.5	2.2	73.4	19.8
chewable tabs - fasted	1.9	2.1	71.0	19.7
chewable tabs - fed	3.3	2.7	63.9	10.9

These data are shown graphically below:



Conclusion: This study showed in fasting conditions, bioequivalence of the chewable tabs to the swallowed tabs, but bioinequivalence of the chewable tabs with the suspension. Specifically, the chewable formulation resulted in a considerably longer Tmax and a lower Cmax (but with the overall AUCinf little changed). The fed state had the expected effects of increasing Tmax and lowering the AUC.

Pharmacodynamic study (protocol AF-95-06)

Because the absorption rate for the chewable tablets was technically inequivalent, but similar, to the suspension, the sponsor was asked to perform a clinical bioequivalence study to evaluate the clinical significance of the different absorption rates.

Design: This was a single-blind, multicenter, randomized, parallel, 8-hour, single-dose study of the antipyretic efficacy of the chewable 50mg ibuprofen tabs with the currently marketed ibuprofen 20mg/ml suspension dosed at approximately 7.5mg/kg. Ninety-three children, ages 2-11, with baseline fever of 101.0-103.9 degree F po or 101.5-104.9 degree F pr, were enrolled and stratifying on $\leq$ versus > 102.5 po or 103.5 pr temperatures. Temperature was measured hourly, with rescue medication ("as determined by the investigator") administered -- and "treatment failure" status declared -- if the temperature increased 1 degree F over baseline, or if it exceeded 104.9 F (pr) or 103.9 F (po), or if there was no temparature fall by 2hr after dosing.

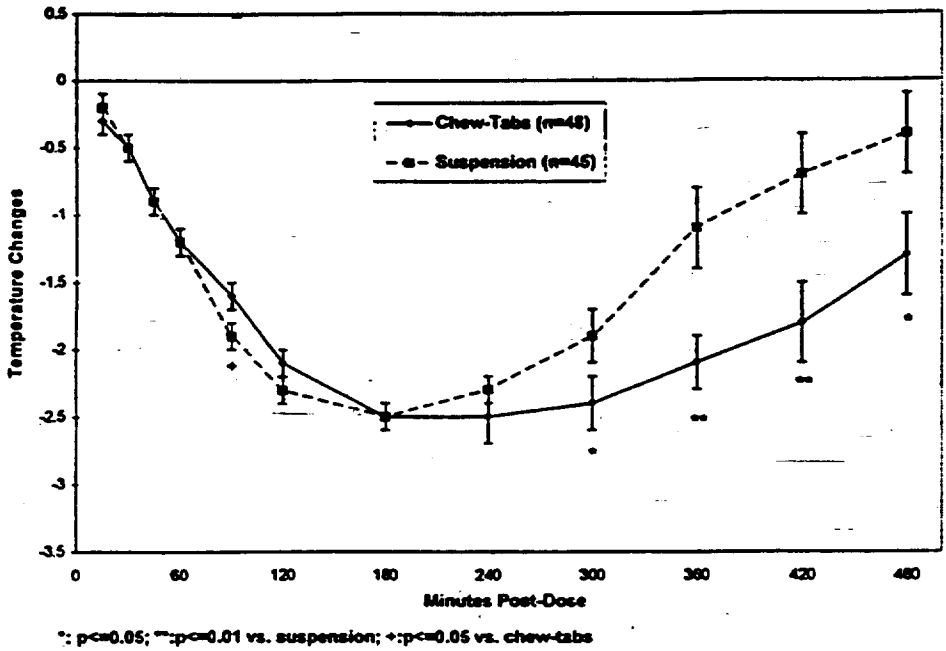
Results: Ninety-one patients were included in the efficacy analysis, one lost from each group (one for an incorrectly calculated dose given, another for Proventil given just after dosing). The results of the primary analysis, an intent-to-treat of time-weighted sum of temperature differences from baseline, are shown in the table below.

Table S.1. AF-95-06 Time-Weighted Sum of Temperature Differences from Baseline - Intent-to-Treat Subjects (Means and Standard Deviations)

Treatment (Sample Size) (a)	Time Points (in Hour)				
	2	4	6	8	Peak Difference
Ibu. 7.5mg/kg(chew - tab) (n=48)	-2.6 (1.0)	-7.5 (2.5)	-11.9 (5.3)	-14.9 (8.2)	-3.1 (1.0)
Ibu. 7.5mg/kg(suspension) (n=45)	-2.8 (1.3)	-7.6 (2.8)	-10.5 (4.8)	-11.6 (7.5)	-2.9 (0.9)
Treatment P-value (b)	0.393	0.840	0.057	0.015	0.053
Trt*Site P-value (b)	0.886	0.374	0.149	0.211	0.069
Trt*Base (b)	0.087	0.839	0.258	0.729	0.131
RMS Error (b)	0.842	2.365	4.666	7.448	0.847

(a) Represents the number of subjects for efficacy based on extrapolated data.
(b) Model: Sum = μ + Trt + Site + Base + Trt*Site + Trt*base + Error

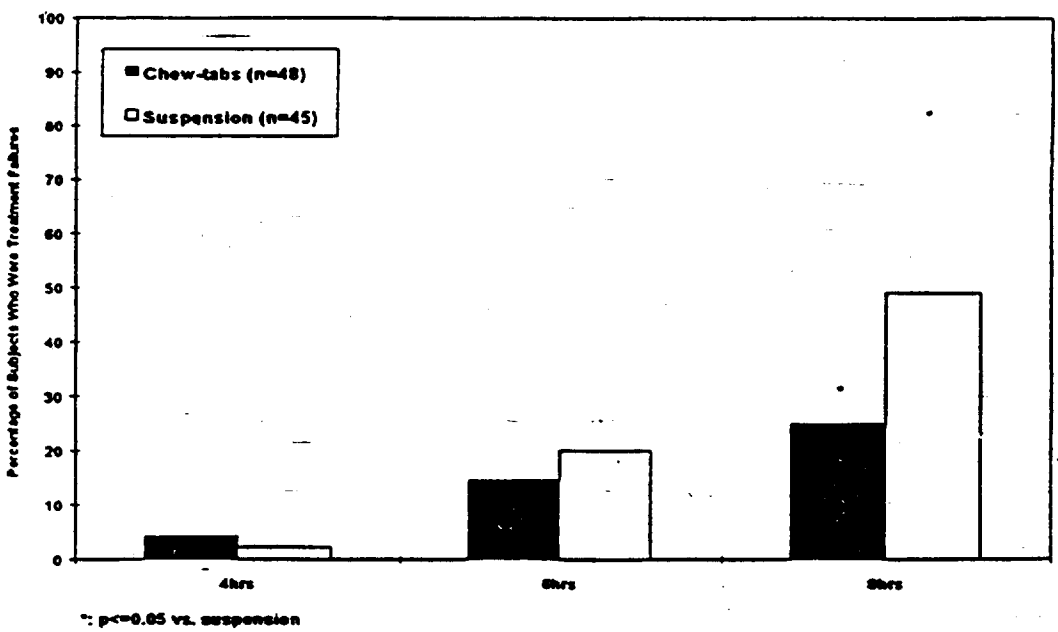
These data are shown graphically below:



*: p<=0.05; **:p<=0.01 vs. suspension; +:p<=0.05 vs. chew-tabs

By this analysis, the chewable is at least as efficacious as the suspension. In particular, antipyresis is virtually identical for the first three to four hours. Thus, the slower absorption does not translate into any clinically detectable slower antipyretic effect. The later timepoints show superiority of the chewable tablets compared to the suspension, but interpretation of later timepoint data is possibly confounded by "treatment failure" (defined above) dropouts. By the 8-hour end of the study 25% of the chewable tab patients and 49% of the suspension patients were "treatment failures". These are shown graphically below.

Proportion of Subjects Who Were Treatment Failures



*: p<=0.05 vs. suspension

Conclusion: These data demonstrate comparable antipyresis efficacy of the chewable and suspension formulations. Thus, despite PK differences in absorption, they are clinically acceptably similar during the absortion phase, should be considered clinically bioequivalent, and merit approval with labelling to be determined by the OTC division.

/S/

Kent Johnson, MD
February 24, 1998

/S/ 7-23-98

CC: Orig NDA 20,944
HFD-550
HFD-340
HFD-550/PM/
HFD-550/Chem/
HFD-550/Pharm/
HFD-550/MO/Johnson

MEDICAL OFFICER UPDATE
NDA 20,944

The April 17,1998, communication from the sponsor did not contain any new safety information. Therefore, no further medical input is forthcoming at this time.

/S/ Niska

Kent Johnson, MD
Medical Officer
December 15, 1998

/S/ 12-16-98

CC:
NDA 20-944
HFD-550/ D.V. File
HFD-550/ Johnson
HFD-550/ Geick

APPEARS THIS WAY
ON ORIGINAL