CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-448

BOEQUIVALENCE REVIEW(S)

NDA 20-448 Submission Date: 3-14-94, 5-20-94 and 11-16-94
Loperamide HCl Chewable Tablet, 2 mg
IMODIUM® A-D CHEWABLE TABLET
Sponsor: McNeil Consumer Products Company

Priority: 3S
Type of Submission: NDA, New Dosage Form **Reviewer:** Rajendra S. Pradhan

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Synopsis: The sponsor has adequately studied the bioequivalence between the reference formulation; Imodium® Capsules and the test formulation; Loperamide HCl Chewable Tablets. The new chewable dosage form was developed as an alternative oral dosage form to the Imodium® A-D Liquid and Caplet. No clinical study other than the bioequivalence study was performed in support of this NDA. The Division of Scientific Investigation (DSI) has initiated an audit of this pivotal bioequivalence study (Study 118).

Recommendation: The sponsor's NDA 20-448 is acceptable to the Division of Biopharmaceutics provided comments 1 and 2 are satisfactorily addressed by the sponsor and the DSI's audit of the bioequivalence study (Study 118) is satisfactory.

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Comments (to be sent to the sponsor):

1. It is noted that the study protocol states: "The tablets will be thoroughly chewed into small particles before swallowing. The mouth will be rinsed three times with portions of the total 200 ml water required with dosing as indicated in Section F.4.a.2. The administrator will varify with the subject that no particles remain in his mouth and record this check on the Case Report Form (CPMD-499)".

   However, the proposed label has the following statement: "Convenient and easy to take without water".

   Considering the way the sponsor conducted the present study, one simply can not evaluate the bioavailability of loperamide chewable tablet administered under the condition as stated in the proposed labelling i.e. without water.

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Loperamide HCl has poor bioavailability probably because of the poor absorption and/or high first-pass metabolism of the drug. The Division of Biopharmaceutics is concerned about the possible buccal absorption with this dosage form when taken without water.

If the drug is to be administered without water, the sponsor has not adequately addressed the safety issue of buccal absorption of loperamide from this dosage form. The statement in the proposed labeling needs to be justified by the firm. Alternatively, the labeling needs to be modified to reflect the study conditions, i.e." take the dosage form with water".

2. The Division of Biopharmaceutics recommends the following product release specifications:
Method:

Comments (to the Medical Officer):

Drowsiness or dizziness, one of the adverse effect of loperamide, could be due to the systemic exposure. The Division of Biopharmaceutics is concerned about a possible increase of this adverse effect if buccal absorption occurs with this formulation.

The dissolution profile of loperamide HCl chewable tablet is significantly influenced by the pH of the dissolution medium. The formulation coated with a pH-sensitive polymer has optimum dissolution rate at pH around 5, but becomes insoluble at the pH of 7. In patients with diarrhoea, it is suspected that due to the increased GI motility, the tablets might reach the intestine so quickly that the drug never gets released. Similarly, food and antacids can influence the pH of GI tract and have effect on the bioavailability and/or effectiveness of this formulation.

3-13-95

Rajendra S. Pradhan, Ph.D.
Division of Biopharmaceutics, Branch II

FT initialed by 3/13/95
Mei-Ling Chen, Ph.D.

cc: NDA 20-448, HFD-180, HFD-427 (Pradhan, MChen), HFD-426 (Fleischer), Chron, Division, Drug, Reviewer, HFD-19 (FOI), HFD-340 (Viswanathan)

Appendix I

Title: A single dose comparison of new experimental loperamide HCl Chewable Tablets with Imodium® capsules in the fasted state.

Investigator and Site:

Study Dates: July 11 to July 25, 1992

Objective: To determine whether experimental Loperamide HCl Chewable Tablets 2 mg, Batch C-130-9H are bioequivalent to the currently marketed Imodium® capsules 2 mg.

Investigator and Site:

Study Dates: July 11 to July 25, 1992

Study Design: The study had a single-dose, open-label, randomized two-way crossover design.

Treatment A 12 mg loperamide HCl as six Loperamide HCl Chewable Tablets 2 mg (Batch C-130-9H), dosed after fasting.
Treatment B 12 mg loperamide HCl as six Imodium® Capsules, 2 mg, dosed after fasting.

Washout time: 14 days between treatments.

Subjects: Thirty-eight adult males out of forty-two that enrolled, completed the study and were included in the pharmacokinetic analysis. Subject 9 was dropped from the study due to an ear

infection before Period 2. Subject 22 discontinued for personal reasons before Period 2. Subject 31 was dropped from the study due to problems with blood draws. The plasma concentration data for subject 38 precluded determination of K_{el} following treatment A. Therefore, his data from neither treatment A nor B were included in the statistical analysis.

Data Analysis: Errors[1] at the clinical contract facility in handling the 4 hr blood samples from some subjects have made certain plasma concentrations questionable. For this reason, the sponsor has conducted three different statistical analysis.

1 all subjects (n=38), with all plasma samples included;
2 all subjects (n=38), with the 4 hr data points removed;
3 only those subjects with complete plasma concentration data sets (n=26).

Results: Table 1 summarizes pharmacokinetic parameters for this study. Tables 2, 3 and 4 illustrate the bioequivalence-analysis, carried out in three different ways. Figures 1, 2 and 3 show mean plasma concentration versus time profile for all subjects with all plasma samples, all subjects with four-hour sample omitted and those subjects with complete profiles, respectively. The sponsor, in order to determine if chewable dosage form gives rise to buccal absorption, analyzed the AUC from time zero to time for Cmax (AUCmax) in the twenty-six subjects for whom all concentration data were available. The results of this analysis are included in Table 2.

Conclusions: The 90% confidence intervals (two one-sided t tests procedure at $\alpha = 0.05$) for each parameter (LCmax, LAUC, LAUCinf) of the test formulation were within 80 to 125% of the corresponding reference mean. Therefore, based on the study results, IMODIUM® A-D Chewable Tablet (Formula C-130-9H), 2 mg, is bioequivalent to IMODIUM® Capsule, 2 mg (Janssen Pharmaceutica).

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1. Please refer to Supplement #1 and #2

C-130/JAS/11

[redacted].1 Summary of *In Vivo* Data for Bioavailability Study 118

Study Number	Route	Dose	N	Mean (± S.D.) [C.V.%] AUC (ng·hr/mL)	LAUC	AUC$_{INF}$ (ng·hr/mL)	LAUC$_{INF}$	C$_{MAX}$ (ng/mL)	LC$_{MAX}$	T$_{MAX}$ (hr)	k_{el} (1/hr)	$t_{1/2}$ (hr)
118	oral	12 mg loperamide HCl as six 2-mg Loperamide HCl Chewable Tablets (C-130-9H) after fasting	38	33.38 (12.46) [37.3]	3.440 (0.380) [11.1]	42.70 (16.40) [38.4]	3.683 (0.388) [10.5]	1.73 (0.60) [34.7]	0.493 (0.343) [69.6]	5.87 (1.83) [31.2]	0.0373 (0.0106) [28.4]	19.93 (5.13) [25.7]
		12 mg loperamide HCl as six 2-mg Imodium® Capsules after fasting	38	34.24 (12.51) [36.5]	3.463 (0.391) [11.3]	41.53 (14.64) [35.2]	3.662 (0.371) [10.1]	1.88 (0.72) [38.3]	0.556 (0.407) [73.3]	6.18 (2.37) [38.4]	0.0407 (0.0094) [23.1]	17.73 (3.34) [18.8]
		12 mg loperamide HCl as six 2-mg Loperamide HCl Chewable Tablets (C-130-9H) after fasting	38[†]	33.24 (12.63) [38.0]	3.433 (0.391) [11.4]	42.57 (16.58) [39.0]	3.678 (0.396) [10.8]	1.59 (0.64) [40.2]	0.392 (0.393) [100.2]	6.63 (1.73) [26.1]	0.0373 (0.0106) [28.4]	19.93 (5.13) [25.7]
		12 mg loperamide HCl as six 2-mg Imodium® Capsules after fasting	38[†]	34.35 (12.77) [37.2]	3.463 (0.399) [11.5]	41.64 (14.86) [35.7]	3.663 (0.378) [10.3]	1.80 (0.69) [38.3]	0.513 (0.403) [78.5]	6.53 (2.24) [34.3]	0.0407 (0.0094) [23.1]	17.73 (3.34) [18.8]
		12 mg loperamide HCl as six 2-mg Loperamide HCl Chewable Tablets (C-130-9H) after fasting	28[††]	33.39 (13.60) [40.7]	3.432 (0.403) [11.7]	42.21 (16.92) [40.1]	3.667 (0.403) [11.0]	1.61 (0.62) [38.5]	0.412 (0.360) [87.4]	6.15 (1.91) [31.1]	0.0385 (0.0107) [27.8]	19.19 (4.67) [24.3]
		12 mg loperamide HCl as six 2-mg Imodium® Capsules after fasting	26[††]	33.74 (12.96) [38.4]	3.442 (0.410) [11.9]	41.20 (14.99) [36.4]	3.650 (0.386) [10.6]	1.78 (0.68) [38.2]	0.500 (0.396) [79.1]	6.31 (2.68) [42.5]	0.0414 (0.0106) [25.6]	17.61 (3.69) [21.0]

[†] 4 Hour plasma sample omitted from analysis.

[††] Subjects with complete plasma profiles included in analysis (Subjects 5, 6, 8, 10, 11, 12, 15, 16, 23, 25, 27 and 28 omitted).

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Table ~~8-2-1~~ Key Pharmacokinetic Parameters of Loperamide in 26 Subjects (subjects with correct complete plasma data sets)

Parameter	Mean[1] (n = 26) C-130-9H (12mg, fasted state)	Mean[1] (n = 26) IMODIUM® Capsules (12mg, fasted state)	90% Confidence Intervals (2 one-sided t-tests)	Pr > |T|	Power (%)
Cmax	1.61	1.80	76.8 to 102.8	0.192	71.2
Tmax	6.16	6.27	86.9 to 109.6	0.795	82.4
AUC	33.61	34.12	86.1 to 110.9	0.839	75.4
AUC0-inf	42.55	41.65	90.8 to 113.6	0.747	82.1
Kel	0.0381	0.0415	84.3 to 99.4	0.077	98.9
T1/2	19.37	17.58	102.3 to 118.1	0.038	98.3
LCmax	0.415	0.513	80.4 to 102.4	0.182	77.2
LAUC	3.444	3.453	88.3 to 111.1	0.884	81.5
LAUC0-inf	3.679	3.661	91.5 to 113.2	0.775	87.0
AUC0-max	5.84	6.52	71.7 to 105.4	0.262	50.0
LAUC0-max	1.603	1.797	69.5 to 98.2	0.074	48.0

[1] Mean values are the least square means. These will not match the arithmetic means listed in other tables due to unbalanced study design.

Table ~~6.2.2.2~~ 3 **Key Pharmacokinetic Parameters of Loperamide in 38 Subjects (subjects with 4 hour plasma data removed)**

Parameter	Mean[1] (n = 38) C-130-9H (12mg, fasted state)	Mean[1] (n = 38) IMODIUM® Capsules (12mg, fasted state)	90% Confidence Intervals (2 one-sided t-tests)	Pr > |T|	Power
Cmax	1.61	1.82	79.0 to 97.8	0.044	93.8
Tmax	6.60	6.49	93.3 to 110.0	0.742	97.4
AUC	33.51	34.61	88.2 to 105.4	0.539	96.7
AUC0-inf	42.83	41.90	94.3 to 110.1	0.639	98.4
Kel	0.0372	0.0409	84.9 to 97.1	0.018	99.9
T1/2	19.97	17.67	106.0 to 120.0	0.004	99.6
LCmax	0.404	0.524	80.8 to 97.3	0.035	94.2
LAUC	3.444	3.471	89.7 to 105.7	0.585	97.8
LAUC0-inf	3.687	3.670	94.4 to 109.8	0.697	99.0

[1] Mean values are the least square means. These will not match the arithmetic means listed in other tables due to unbalanced study design.

Table ~~6.2.2.3~~ 4 **Key Pharmacokinetic Parameters of Loperamide in 38 Subjects (subjects with all plasma data included)**

Parameter	Mean[1] (n = 38) C-130-9H (12mg, fasted state)	IMODIUM® Capsules (12mg, fasted state)	90% Confidence Intervals (2 one-sided t-tests)			Pr > |T|	Power
Cmax	1.74	1.91	80.7	to	101.2	0.144	89.4
Tmax	5.90	6.14	86.4	to	105.7	0.498	92.4
AUC	33.64	34.48	89.0	to	106.1	0.633	96.8
AUC0-inf	42.96	41.77	95.0	to	110.7	0.547	98.5
Kel	0.0372	0.0409	84.9	to	97.1	0.018	99.9
T1/2	19.97	17.67	106.0	to	120.0	0.004	99.6
LCmax	0.495	0.570	83.6	to	102.9	0.229	88.7
LAUC	3.451	3.471	90.5	to	106.2	0.683	98.3
LAUC0-inf	3.693	3.669	95.1	to	110.2	0.593	99.2

[1] Mean values are the least square means. These will not match the arithmetic means listed in other tables due to unbalanced study design.

Figure 6.2.1

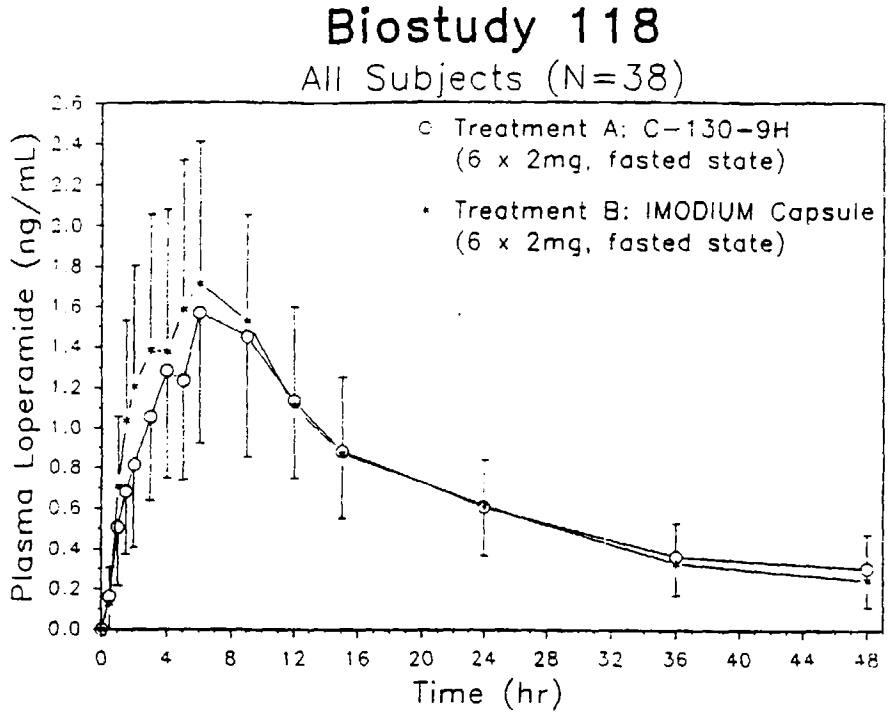


Figure 6.2.2

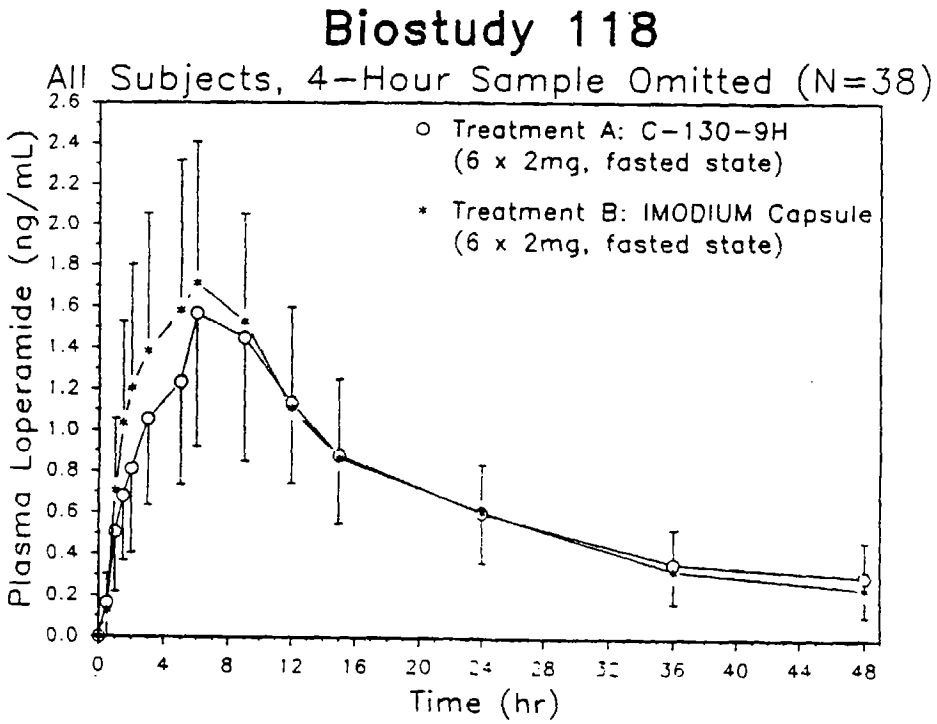
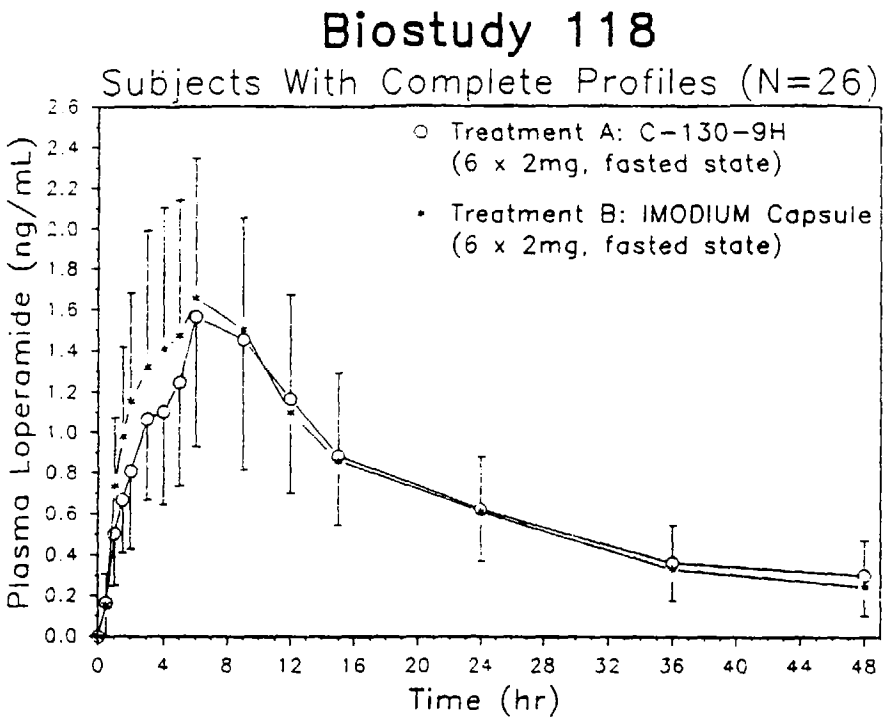


Figure 6&2.3



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