CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-448

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

[redacted]

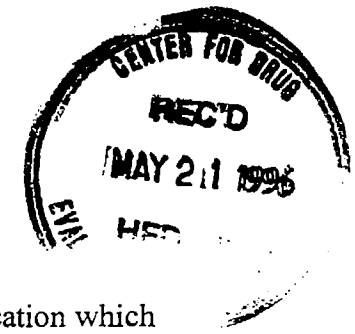
Clinical Pharmacology & Biopharmaceutics Review

NDA 20-448, amendment (AC) Submission Date: 12-21-95
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

Background: In the Office of Clinical Pharmacology and Biopharmaceutics (OCPB), Division of Pharmaceutical Evaluation II (DPE-II) review of the NDA 20-448, dated 03-13-96, following comment was conveyed to the sponsor.

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



This comment was made in response to the sponsor's proposed dissolution specification which suggested the in-vitro dissolution to be carried out on crushed tablet and specification to be set to (rest of the conditions being same as above). The comment was made after reviewing the in-vitro dissolution data that was submitted by the sponsor on crushed tablet, whole table and half tablet (broken at the score).

The Imodium® A-D Chewable Tablet is manufactured (formulation Appendix I).

The sponsor in the stability studies found that when the tablets were stored in the blister package at 40°C/75% RH for 3 months, dissolution rate of whole tablets decreased significantly, while crushed tablet dissolution rate showed either slight or no change. Additionally the sponsor conducted disintegration studies on tablets stored in the blister package, Blister package tablets stored at 40°C/75% RH yielded longer disintegration times than tablets stored at 25°C/60% RH (Data in Appendix I).

The sponsor is proposing that the observed effect on dissolution of whole tablets is a function of the tablet's excipient composition and not a result of changes

Therefore, a dissolution specification on crushed loperamide HCl chewable tablets should be adopted.

Comments: The stability data suggests that storing the loperamide HCl chewable tablet at higher temperature than room temperature and at higher relative humidity causes a change in tablet's excipient composition. Also, the observed decrease in the dissolution and disintegration rate do not suggest any compositional change in loperamide granules. However, performing a in-vitro dissolution on a crushed tablet raises a red flag. This is because the process of crushing is not a standardized and validated process. Also, crushing can modify/manipulate the in-vitro dissolution of tablets. Clinically, different people are going to chew a tablet differently and therefore there are no common parameters on which one can simulate an in-vitro crushing procedure. One alternative is to mention in the label, under "How to Administer" section, the chewing time, ie. Chew the tablet for 2 minutes or 4 minutes etc. This way the sponsor can perform the crushing in some standardized way prior to carrying out the dissolution. Stating the chewing time in the label will reduce the variation in chewing by the patients.

Recommendation: The Division of Pharmaceutical Evaluation II accepts the dissolution specification proposed by the sponsor provided the sponsor addresses the following:

5-21-96

Rajendra S. Pradhan, Ph.D.
Division Pharmaceutical Evaluation II

FT initialed by LCK
Lydia Kaus, Ph.D. 5/21/96

cc: NDA 20-448, HFD-180, HFD-870 (Pradhan, Kaus, MChen), HFD-860 (Malinowski), HFD-880 (Fleischer), HFD-850 (Chron, Drug, Reviewer), HFD-205 (FOI), HFD-340 (Viswanathan), HFD-850 (Lesko)

Appendix I

THIS PAGE
WAS
DETERMINED
NOT
TO BE
RELEASABLE

Table I

Mean % Dissolved IMODIUM A-D® Chewable Tablets, 2mg Batch C-130-9I, 30 minutes, blisters		
Storage	Crushed Tablet	Whole Tablet
Initial	98%	100%
1 Mo 40°C/75%RH	100%	93%
2 Mo 40°C/75%RH	98%	75%
3 Mo 40°C/75%RH	98%	64%
3 Mo 30°C	94%	Not Tested

Table II

Mean % Dissolved IMODIUM A-D® Chewable Tablets, 2mg Batch C-130-9N, 30 minutes, blisters (8584)		
Storage	Crushed Tablet	Whole Tablet
Initial	97%	99%
1 Mo 40°C/75%RH	96%	84%
2 Mo 40°C/75%RH	93%	71%
3 Mo 40°C/75%RH	102%	75%
3 Mo 25°C/60%RH	94%	97%

C130/mmb/7

00 00000

Table III

Mean % Dissolved IMODIUM A-D® Chewable Tablets, 2mg Batch C-130-9O, 30 minutes, blisters (8585)		
Storage	Crushed Tablet	Whole Tablet
Initial	92%	92%
1 Mo 40°C/75%RH	93%	79%
2 Mo 40°C/75%RH	90%	74%
3 Mo 40°C/75%RH	85%	73%
3 Mo 25°C/60%RH	93%	92%

Table IV

Mean % Dissolved IMODIUM A-D® Chewable Tablets, 2mg Batch C-130-9P, 30 minutes, blisters (8586)		
Storage	Crushed Tablet	Whole Tablet
Initial	100%	99%
1 Mo 40°C/75%RH	95%	66%
2 Mo 40°C/75%RH	92%	61%
3 Mo 40°C/75%RH	96%	57%
3 Mo 25°C/60%RH	96%	96%

Table V

Disintegration Time IMODIUM A-D® Chewable Tablets, 2mg Batch C-130-9N Blister Packaged		
Storage Conditions	Testing Interval	Disintegration Time (low, high) n = 6
	Initial	min
40°C/75%RH	2 Weeks	min
40°C/75%RH	4 Weeks	min
25°C/60%RH	4 Months	min