OTC MEDICAL OFFICER'S REVIEW

Drug name: **Overnight Relief Perdiem®**
Fiber Therapy Perdiem®
OTC Tracking #: **2624**
Sponsor: **Novartis Consumer Healthcare, Inc.**
Pharmacologic Category: **Laxative**
Proposed Indication: **Laxative**
Dosage Form and Route of Administration:
One to two rounded teaspoonfuls one to two times a day should be placed in the mouth and swallowed with at least 8 ounces of cool liquid
Assigned to the reviewer: **April 30, 2001**
Review date: **May 23, 2001**
Reviewer: **Daiva Shetty, MD**

Background

This is the medical officer's clinical safety review of Perdiem® drug products (Overnight Relief Perdiem® and Fiber Therapy Perdiem®).

Perdiem® is a psyllium containing bulk forming laxative, and is currently approved for over-the-counter use for relief and prevention of constipation.

Since the introduction of Perdiem® products into the market place in 1979, the agency has been receiving reports of esophageal obstruction associated with their use. Safety assessment of these products has been revisited by the agency on several occasions. The Division of Epidemiology and Surveillance on March 9, 1990 performed detailed safety review. According to this review, there were total of 61 actual number of cases of esophageal obstruction reported to the sponsor and the agency from 1979 to 1989. There were total of 15 similar cases reported to the agency between 1989 to present.

The agency had concerns about the continued OTC marketing of this product as it was labeled and formulated. In its letter to the sponsor (Rorer Pharmaceutical Corporation) on August 6, 1990, the agency suggested that Perdiem® be the subject of a new drug application (NDA) for the use under medical supervision. As an alternative, to retain OTC status, the agency suggested that the product be reformulated so that it may be suspended in no less than 8 ounces of liquid per dose prior to consumption.

The following actions have been taken by the manufacturer, trying to resolve the problem:

- In 1985, the directions for use were modified to emphasize the need to have adequate fluid intake.

- A patient package insert was placed inside each can stressing the importance of taking sufficient liquid.
- A "Dear Doctor" letter was sent to U.S. physicians, calling attention to the need for adequate fluid intake to avoid the risk of esophageal obstruction.

After the institution of these changes, the number of adverse event reports decreased. As per sponsor's estimation, the incidence of esophageal obstruction in 1989 was approximately 1:20 million doses compared to 1:5 million doses sold in 1985[1].

The agency also has received other reports indicating that esophageal obstruction and asphyxiation have been associated with the ingestion of water-soluble gums, hydrophilic gums, and hydrophilic mucilloids, including psyllium. Therefore, on August 26, 1993, the agency has issued the following new warning to be required for psyllium products (21CFR201.319):
"WARNING: (Select one of the following, as appropriate: TAKE or MIX) THIS PRODUCT WITH AT LEAST 8 OUNCES (A FULL GLASS) OF WATER OR OTHER FLUID. TAKING THIS PRODUCT WITHOUT ADEQUATE FLUID MAY CAUSE IT TO SWELL AND BLOCK YOUR THROAT OR ESOPHAGUS AND MAY CAUSE CHOKING. DO NOT TAKE THIS PRODUCT IF YOU HAVE EVER HAD DIFFICULTY IN SWALLOWING. IF YOU EXPERIENCE CHEST PAIN, VOMITING, OR DIFFICULTY IN SWALLOWING OR BREATHING AFTER TAKING THIS PRODUCT, SEEK IMMEDIATE MEDICAL ATTENTION."

Despite all of these warnings and labeling changes, the agency continues to receive reports of the esophageal obstruction. Therefore, the Office of Compliance (HFD-312) in January 2001 requested limited inspection of manufacturer. During the inspection, adverse event (AEs) reports received from January 1999 to January 2001 for Overnight Relief Perdiem® and Fiber Therapy Perdiem® were collected. In addition, on November 17, 2000, the Division of Drug Risk Evaluation I (HFD-430) performed their postmarketing safety data review which covered entire Adverse Event Reporting System (AERS) database and the medical literature for similar reports.

This review summarizes Novartis Health Care Inc. and HFD-430 safety data for the period of 1999 to January 2001.

Results

Reports of AEs associated with Perdiem® products related to esophageal obstruction, reported to the sponsor and the FDA AERS between January 1999 and January 2001, have been summarized and analyzed.

A total of 43 adverse events were available for analysis. All of the events but one (#4) occurred in the United States. The cases are summarized in Appendix 1.

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[1] Letter from the Rorer Pharmaceutical Corporation to the agency. Docket No.78N-036L. Comment No.C00100. August 28, 1990.

Majority of the cases (1-42) came from the sponsor's database. Approximately 700 spontaneous adverse event reports were received by Novartis Health Care Inc. during the last 2 years, of which 42 (6%) were related to esophageal obstruction. Four (#9, 28, 38, 40) out of total of five cases collected by FDA's AERS, had been reported in the sponsor's adverse event database. In addition, one of those cases (#40) had been published. In summary, there were total of 43 unduplicated cases in 42 patients associated with Perdiem® products causing esophageal obstruction, 25 of which were reported in 1999, 17 in 2000, and 1 case in 2001.

There were no deaths reported. Twelve out of total of 43 cases were assessed by the sponsor as serious events, requiring hospitalizaton, ER visit and/or the need for the invasive procedure. The reactions of the events were coded as vomiting, dysphagia, esophageal obstruction, foreign body sensation, dyspnea, chest or abdominal pain. After the review of each case descriptive narrative, symptoms of all 43 cases were assessed as related to esophageal obstruction.

Most of the subjects experiencing the esophageal obstruction were in the middle age category. The age ranged from 23 to 87 years, with the mean of 65, and median of 69 years. Age was not reported in 12 cases. Information on gender was available for all cases with 22 being females and 21 males.

Most of the people taking Perdiem were following the directions on the label. Information on the dose taken was available in 36 out of 43 cases. Five subjects exceeded recommended single maximum dose of the product specified on the label. Amount of fluid intake with the product was described in 35 cases. Majority of the subjects (27 out of 35) took sufficient fluid with the product. Insufficient amount of fluid intake may have contributed to the esophageal obstruction in 7 cases. Other possible underlying conditions as risk factors were identified in 6 subjects: 1 had esophageal cancer, 3 had esophageal narrowing or stricture, and 2 had hiatal hernia.

Outcomes of the cases were as follows:

- 10 subjects required hospitalization (all serious),
- 4 subjects went to Emergency Room (one serious),
- 10 subjects underwent endoscopy as diagnostic (n=1, non-serious) or therapeutic procedure (n=9, all serious),
- 32 events resolved without intervention, or outcome is unknown.

Conclusions

This review was performed on the limited data. In order to assess the safety of Perdiem® products, postmarketing data for the entire marketing history is required. In addition, information on changes in formulation and manufacturing practices during the course of the years, in relationship to these adverse events, should be evaluated.

Based on the data reviewed, in the opinion of this reviewer, it seems that there is still a significant safety problem with esophageal obstruction associated with the use of Perdiem® products. Multiple labeling changes in the past did not resolve this problem, and most probably, will not add more to the safety of these products in the future. During the first 10 years of marketing, there was 61 case of esophageal obstruction reported compared to 43 cases during the last 2 years alone. Even though all of the cases were non-fatal, a quarter (n=10) of them led to hospitalization and/or the need for the invasive procedure (n=10). The incidence rate of these events cannot be estimated because of the nature of the reporting system, and unknown number of patients using the product.

Recommendations

1. Perdiem® products should not be marketed under the Laxative Monograph. The safety and efficacy for these products should be assessed under a NDA.
2. Perdiem® products should be reformulated into a safer formulation. The sponsor should be requested to submit the data on formulation and manufacturing changes for these products over the years of marketing history.
3. Entire postmarketing safety data, including foreign data, should be re-evaluated and monitored yearly as for any NDA drug product.

Signed 6/1/2001

Daiva Shetty, M.D.
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Signed 6/1/2001

Linda M. Katz, M.D., M.P.H.
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Appendix 1. Cases of Esophageal Obstruction Associated with PERDIEM® (January 1999- January 2001)

	Age Gender	Year of onset/report	Dose	Reaction	Water Ingested	Relevant History	Endoscopy	Hospitalization	Assessed as serious
1	59 F	9/2000	1 tsp	Vomiting, Nausea	As directed	None stated	No	No	No
2	81 M	8/1999	2 ½ tsp	Dysphagia, Foreign body	As directed	Esophageal cancer	UNK	Yes	Yes
3	87 M	9/1999	1 tsp	Dysphagia	As directed	None stated	No	No	No
4	76 M	2/1999	UNK	Esophageal obstruction	Unknown	None stated	UNK	Yes	Yes
5	? M	4/2000	3 tsp	Dysphagia, Vomiting	As directed	None stated	No	No	No
6	62 M	3/2000	1 tsp	Dysphagia	As directed	None stated	No	No	No
7	59 F	1/2001	2 tsp	Dysphagia	Insufficient	Esophageal stricture	No	No	No
8	74 F	8/2000	1 tblsp	Dysphagia, Foreign body	As directed	None stated	No	No	No
9	83 F	9/2000	1-2 tsp	Dysphagia, Foreign body, Vomiting	As directed	None stated	Yes	Yes	Yes
10	? F	8/2000	1 tsp	Chest pain, Foreign body, Vomiting	Insufficient	UNK	UNK	No	No
11	60 F	1/2000	1 tsp	Foreign body, Abd. pain	As directed	None stated	No	No	No
12	? M	11/2000	UNK	Dysphagia	Unknown	None stated	Yes	Yes	Yes
13	69 M	8/2000	1 tsp	Dysphagia, Foreign body, Esophagitis	As directed	Esophageal stricture Hiatal hernia	Yes	No	No
14	46 F	8/2000	1 tblsp	Dysphagia, Foreign body	Insufficient	None stated	No	No	No
15	40 M	6/2000	2 tsp	Dysphagia, Foreign body	Unknown	None stated	Yes	Yes	Yes
16	56 F	6/2000	1 tsp	Dysphagia, Vomiting	As directed	None stated	No	No	No
17	? F	9/2000	1 tsp	Foreign body	As directed	UNK	No	No	No
18	? F	7/2000	1 tsp	Dysphagia, Foreign body, Esoph. Ulceration, hypotension	As directed	UNK	Yes	Yes	Yes
19	? M	10/1999	1 tsp	Dysphagia,	Unknown	UNK	No	No	No
20	30 F	8/1999	1 tsp	Dysphagia, Dyspnea	Insufficient	None stated	No	No	No
21	77 M	7/1999	1 tsp	Dysphagia, Eructation	As directed	None stated	No	No	No
22	53 M	5/1999	1-2 tsp	Dysphagia,	As directed	None stated	No	No	No
23	77 M	8/1999	3 tsp	Vomiting, Foreign body	Insufficient	None stated	No	No	No
24	68 M	7/1999	2 tsp	Dysphagia, Nausea	As directed	None stated	No	No	No
25	? F	3/1999	½capful	Dysphagia, Vomiting	Insufficient	UNK	UNK	UNK	No
26	72 F	11/1999	2 tsp	Dysphagia	As directed	Esophagus narrowing	No	Yes	Yes
27	? F	8/1999	2 tsp	Dysphagia	No	UNK	UNK	UNK	No

28	62 F	6/1999	2 tsp	Dysphagia, Dehydration, Abd. Pain, Chest pain	Insufficient	Hiatal hernia	Yes	Yes	Yes
29	? M	4/1999	1 dose	Dysphagia	As directed	UNK	No	No	No
30	23 F	2/2000	1 tsp	Tachycardia, Dyspnea, HTN, Anxiety	As directed	None stated	No	ER	No
31	? F	6/2000	UNK	Dysphagia, Foreign body, Headache	Unknown	Hiatal hernia	Yes	No	Yes
32	? F	3/1999	1 tsp	Dysphagia	Unknown	UNK	UNK	UNK	No
33	83 F	8/1999	2 tsp	Dysphagia	As directed	UNK	No	No	No
34	80 M	10/1999	1 tsp	Dysphagia	As directed	None stated	No	No	No
35	? M	4/1999	UNK	Chest pain, Foreign body	As directed	UNK	No	No	No
36	72 F	7/1999	1 tsp	Dysphagia	As directed	None stated	No	No	No
37	47 M	11/1999	2 tsp	Dysphagia, Foreign body, Dystonia	Insufficient	None stated	No	No	No
38	71 F	8/1999	1 dose	Dysphagia, Dyspnea, Nervousness	Insufficient	None stated	Yes	ER	Yes
39	61 M	1/1999	UNK	Dysphagia	As directed	UNK	UNK	UNK	No
40	69 M	5/1999	UNK	Dysphagia, Bezoar	As directed	Dysphagia	Yes	Yes	Yes
41	71 M	1/1999	1 ½ tsp	Dysphagia, Chest pain, Vomiting	As directed	None stated	No	ER	No
42	71 M	4/1999	1 ½ tsp	Dyspnea, Chest pain, Hiccup	As directed	None stated	No	ER	No
43	67 F	5/2000	UNK	Dyspnea, Dysphagia, Abd. pain	As directed	None stated	Yes	Yes	Yes

CASES OF ESOPHAGEAL OBSTRUCTION ASSOCIATED WITH PERDIEM

CASE	AGE	SEX	LOCATION	DATE OF ONSET (RECEIPT DATE)	DOSE	REACTION	ENDOSCOPED	WATER INGESTED	RELEVANT HISTORY	HOSPITALIZED
1	64	M	PA	Feb-80	UNK	ESOPHAGEAL OBSTRUCTION	YES	FULL GLASS	NONE STATED	NO
2	80	M	LA	Feb-80	UNK	ESOPHAGEAL OBSTRUCTION	UNK	UNK	STRICTURE OF LOWER ESOPHAGUS	NO
3	69	F	AR	Feb-80	UNK	ESOPHAGEAL OBSTRUCTION	NO	UNK	HIATAL HERNIA ESOPHAGEAL REFLUX	YES
4	UNK	F	NY	Jun-80	UNK	ESOPHAGEAL OBSTRUCTION	NO	UNK	HIATAL HERNIA	NO
5	UNK	U	NY	Jun-80	UNK	ESOPHAGEAL OBSTRUCTION	NO	UNK	NONE STATED	NO
6	UNK	F	FL	Jun-80	UNK	ESOPHAGEAL OBSTRUCTION	YES	FULL GLASS	SLIGHT ESOPHAGEAL STRICTURE	NO
7	80	F	CA	Jul-80	UNK	ESOPHAGEAL OBSTRUCTION	YES	UNK	HIATAL HERNIA	NO
8	80	M	NE	Aug-80	UNK	ESOPHAGEAL OBSTRUCTION	NO	LITTLE	NONE STATED	YES
9	UNK	U	CT	Mar-81	UNK	ESOPHAGEAL OBSTRUCTION	YES	UNK	NONE STATED	YES
10	UNK	F	IN	Sep-81	UNK	ESOPHAGEAL OBSTRUCTION	YES	UNK	ESOPHAGEAL STRICTURE	YES
11	UNK	M	KS	Aug-82	UNK	ESOPHAGEAL OBSTRUCTION	YES	UNK	NONE STATED	NO
12	UNK	U	CA	Dec-82	UNK	ESOPHAGEAL OBSTRUCTION	YES	UNK	NONE STATED	NO
13	70	F	NY	Jan-83	UNK	ESOPHAGEAL OBSTRUCTION	YES	UNK	ESOPHAGEAL STRICTURE	YES
14	UNK	F	IL	Nov-82	UNK	ESOPHAGEAL OBSTRUCTION	UNK	UNK	NONE STATED	YES
15	67	U	NC	Jun-83	UNK	ESOPHAGEAL OBSTRUCTION	YES	UNK	DYSPHAGIA	NO
16	UNK	U	PA	Jun-83	3 TSP	ESOPHAGEAL OBSTRUCTION	YES	YES	NONE STATED	YES
17	UNK	F	NY	Jul-83	UNK	ESOPHAGEAL OBSTRUCTION	YES	UNK	NONE STATED	NO

CASES OF ESOPHAGEAL OBSTRUCTION ASSOCIATED WITH PERDIEM

CASE	AGE	SEX	LOCATION	DATE OF ONSET (RECEIPT DATE)	DOSE	REACTION	ENDOSCOPED	WATER INGESTED	RELEVANT HISTORY	HOSPITALIZED
18	UNK	U	PA	Jul-83	6 GM	ESOPHAGEAL OBSTRUCTION	YES	UNK	HIATAL HERNIA SCHATZKI RING	UNK
19	75	F	ME	Aug-83	UNK	ESOPHAGEAL OBSTRUCTION	YES	UNK	HIATAL HERNIA ESOPHAGEAL SPASMS	NO
20	59	U	NY	Sep-83	UNK	ESOPHAGEAL OBSTRUCTION	YES	UNK	SCHATZKI RING	YES
21	UNK	M	NY	Oct-83	UNK	ESOPHAGEAL OBSTRUCTION	NO	UNK	ESOPHAGEAL NARROWING	NO
22	70	M	NY	Nov-83	UNK	ESOPHAGEAL OBSTRUCTION	NO	UNK	ESOPHAGEAL STRICTURE	NO
23	76	M	NJ	Mar-84	UNK	ESOPHAGEAL OBSTRUCTION	YES	UNK	NONE STATED	NO
24	70	M	LA	Apr-84	UNK	ESOPHAGEAL OBSTRUCTION	YES	UNK	NONE STATED	YES
25	51	F	NM	Jun-84	12 GM	ESOPHAGEAL OBSTRUCTION	NO	GLASS	HIATAL HERNIA	NO
26	76	F	TX	Jul-84	24 GM	ESOPHAGEAL OBSTRUCTION	YES	UNK	HIATAL HERNIA	YES
27	60	F	MA	Oct-84	6 GM	ESOPHAGEAL OBSTRUCTION	YES	UNK	ESOPHAGEAL RING	YES
	UNK	U	TN	Nov-84	UNK	ESOPHAGEAL OBSTRUCTION	UNK	UNK	NONE STATED	UNK
29	79	F	TN	Dec-84	2-3 TSP	ESOPHAGEAL OBSTRUCTION	YES	NONE	NONE STATED	NO
30	84	F	GA	Dec-84	UNK	ESOPHAGEAL OBSTRUCTION	UNK	NOT ENOUGH	NONE STATED	UNK
31	UNK	M	GA	Dec-84	UNK	ESOPHAGEAL OBSTRUCTION	UNK	UNK	HIATAL HERNIA	UNK
32	81	M	OH	Aug-84	UNK	ESOPHAGEAL OBSTRUCTION	NO	UNK	NONE STATED	NO
33	68	F	CA	Jan-85	UNK	ESOPHAGEAL OBSTRUCTION	NO	UNK	SMALL HIATAL HERNIA	NO

CASES OF ESOPHAGEAL OBSTRUCTION ASSOCIATED WITH PERDIEM

CASE	AGE	SEX	LOCATION	DATE OF ONSET (RECEIPT DATE)	DOSE	REACTION	ENDOSCOPED	WATER INGESTED	RELEVANT HISTORY	HOSPITALIZED
3	UNK	F	FL	Jan-85	UNK	ESOPHAGEAL OBSTRUCTION	UNK	UNK	SWALLOWING DYSFUNCTION	NO
35	UNK	U	CA	Jan-85	12 GM	ESOPHAGEAL OBSTRUCTION	NO	VERY LITTLE	SLIGHT STRICTURE	NO
36	70	M	PA	Jan-85	12 GM	ESOPHAGEAL OBSTRUCTION	YES	INSUFFICIENT	NONE STATED	YES
37	71	M	MD	Sep-81	12 GM	ESOPHAGEAL OBSTRUCTION	NO	SMALL AMOUNT	ESOPHAGEAL VARICES	NO
38	70	M	TX	Jan-85	UNK	ESOPHAGEAL OBSTRUCTION	NO	LITTLE OR NONE	NONE STATED	NO
39	69	M	TX	Nov-84	6 GM	ESOPHAGEAL OBSTRUCTION	NO	UNK	NONE STATED	NO
40	UNK	M	TX	Oct-83	UNK	ESOPHAGEAL OBSTRUCTION	NO	HOT COFFEE	NONE STATED	NO
41	UNK	U	TN	May-85	UNK	ESOPHAGEAL OBSTRUCTION	UNK	UNK	SCHATZKI RING	UNK
42	UNK	F	SC	Sep-85	UNK	ESOPHAGEAL OBSTRUCTION	NO	UNK	SWALLOWING PROBLEMS	NO
43	56	F	FL	Oct-85	12 GM	ESOPHAGEAL OBSTRUCTION	UNK	UNK	NONE STATED	NO
44	83	U	PA	May-85	6 GM	ESOPHAGEAL OBSTRUCTION	UNK	AS DIRECTED	NONE STATED	YES
45	56	F	TX	May-86	UNK	ESOPHAGEAL OBSTRUCTION	YES	UNK	NONE STATED	NO
46	UNK	U	TN	Jul-86	UNK	ESOPHAGEAL OBSTRUCTION	UNK	UNK	NONE STATED	UNK
47	71	F	IN	Oct-86	6 GM	ESOPHAGEAL OBSTRUCTION	YES	GLASS	NONE STATED	NO
48	85	F	MO	Oct-87	12 GM	ESOPHAGEAL OBSTRUCTION	YES	4 OZ	ESOPHAGEAL STRICTURE	NO
49	UNK	U	TX	Oct-88	UNK	ESOPHAGEAL OBSTRUCTION	YES	UNK	NONE STATED	UNK
50	UNK	U	TX	Oct-88	UNK	ESOPHAGEAL OBSTRUCTION	YES	UNK	NONE STATED	UNK

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CASES OF ESOPHAGEAL OBSTRUCTION ASSOCIATED WITH PERDIEM

CASE	AGE	SEX	LOCATION	DATE OF ONSET (RECEIPT DATE)	DOSE	REACTION	ENDOSCOPED	WATER INGESTED	RELEVANT HISTORY	HOSPITALIZED
51	UNK	U	TX	Oct-88	UNK	ESOPHAGEAL OBSTRUCTION	YES	UNK	NONE STATED	UNK
52	82	M	IN	Oct-88	12 GM	ESOPHAGEAL OBSTRUCTION	YES	UNK	DYSPHAGIA ESOPHAGEAL MOTILITY DISORDER	YES
53	61	F	OH	Dec-88	UNK	ESOPHAGEAL OBSTRUCTION	UNK	UNK	DYSPHAGIA	YES
54	UNK	M	PA	Oct-85	UNK	ESOPHAGEAL OBSTRUCTION	NO	UNK	HIATAL HERNIA ESOPHAGUS NARROWED	NO
55	UNK	U	PA	Sep-86	UNK	ESOPHAGEAL OBSTRUCTION	UNK	UNK-	NONE STATED	UNK
56	54	M	TN	Mar-88	6 GM	ESOPHAGEAL OBSTRUCTION	YES	UNK	NONE STATED	YES
57	UNK	M	AZ	Jul-87	6 GM	ESOPHAGEAL OBSTRUCTION	YES	UNK	NONE STATED	NO
58	84	F	OR	Feb-88	1 TSP	ESOPHAGEAL OBSTRUCTION	NO	AS DIRECTED	NONE STATED	NO
59	28	M	VA	Mar-84	24 GM	ESOPHAGEAL OBSTRUCTION	YES	UNK	HIATAL HERNIA ESOPHAGITIS DYSPHAGIA	YES
	28	M	TX	Mar-85	12 GM	ESOPHAGEAL OBSTRUCTION	YES	INSUFFICIENT	NONE STATED	YES
61	80	M	AL	Jul-86	1 TSP	ESOPHAGEAL OBSTRUCTION	UNK	UNK	ESOPHAGEAL STRICTURE	YES

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