

**MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

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SUBJECT: OPDRA Postmarketing Safety Review (PID 000607)
Drug: Psyllium Laxative Products (Perdiem, Metamucil, and
Serutan)
Reaction: Esophageal Obstruction and Choking Events

EXECUTIVE SUMMARY

This document summarizes our review of 98 cases of esophageal obstruction and related events associated with the use of psyllium products. The three products involved include Perdiem-78, Metamucil-13, and Serutan-7. We were unable to locate any reports for other OTC bulk forming products. In general, these events occurred in elderly patients many that may have had risk factors for these events. There were more cases of esophageal obstruction with Perdiem, and more choking-related events with Metamucil. Serutan involved both esophageal obstruction as well as choking-related events.

Seventy-eight cases of esophageal obstruction or blockage were temporally related to the use of the Perdiem. The majority of the cases were reported prior to the final monograph in 1994, with only eight reported since that time. Possible risk factors were identified in 52% of the cases, however there were 37 cases with no reported or no apparent risk factors. Twenty-seven cases made reference to appropriate (9) or inappropriate (18) use of the product. The outcomes included one death, 59 that required medical intervention, and 19 that resolved spontaneously.

Thirteen cases of choking-related events (11) and esophageal obstruction

(2) were temporally related to the use of Metamucil products. The choking-related events include choking, difficulty breathing, swelling of the throat, difficulty swallowing, and asphyxia. Possible risk factors were identified in three of the cases. Seven cases made reference to appropriate (3) or inappropriate (4) use of the product. The outcomes include three patients that died, seven that required hospitalization, and three patients whose event resolved spontaneously. Two of the death cases were the result of asphyxiation and one died of laryngotracheal and left main bronchus obstruction.

Seven cases of choking-related events (3) and esophageal obstruction (4) were temporally related to the use of Serutan. All of these are older cases with the latest reported in 1984. One patient had a reported history of esophageal distress. Seven cases made reference to appropriate (2) or inappropriate (4) use of the product. All seven patients were reportedly hospitalized. One patient required surgery to remove the obstruction.

In conclusion, esophageal obstruction requiring invasive medical intervention continues to occur with Perdiem despite the increased warnings regarding use of the products with adequate fluid intake. After discussion between DDRE I and DOTCDP, it was agreed the sponsor be requested to reformulate Perdiem. Esophageal obstruction occurred with Metamucil when it was given concomitantly with other medications. We agree with the DOTCDP that Metamucil powder should be relabeled to avoid use with other medications to facilitate the appropriate use of the product.

INTRODUCTION

The Division of Over-the-Counter Drug Products (DOTCDP) has been aware of esophageal obstruction cases with the water-soluble laxative products, particularly with Perdiem. The manufacturer of Perdiem issued a Dear Doctor letter in February 1985 warning of the potential to obstruct the esophagus, particularly in the presence of esophageal narrowing or when consumed with insufficient fluid. On February 29, 1994, the DOTCDP proposed and finalized the water-soluble gum warning in 201.319 which requires the "choking warning" and specific warnings and directions regarding taking these products with adequate water. Below is the warning required on these products.

"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 difficulty in swallowing. If you experience chest pain, vomiting or difficulty in swallowing or breathing after taking this product, seek immediate medical attention."

During the routine postmarketing safety monitoring of these products, Ann Corken noted several cases of esophageal obstruction requiring invasive medical intervention with both Perdiem and Metamucil products. She brought this to the attention of DOTCDP's Helen Cothran on July 21, 2000. Based on the recent cases, we decided to look at the entire AERS database and the medical literature for similar reports with all psyllium products and to conduct a formal review of this event. We presented these findings to the DOTCDP's medical officers on November 6, 2000

MEDICAL LITERATURE

A MEDLINE search of the English-language literature published from 1966 to 2000 produced five publications describing seven case reports of esophageal obstruction from Perdiem products.¹⁻⁵ These case reports are included in the summary section. There were three additional foreign published cases of esophageal obstruction with granular laxatives.⁶⁻⁸ These were not included in the summary section because it is unknown whether the granular laxative products described in these reports are similar to any of the products marketed in the US. These are briefly summarized below.

- **A 66-year-old man presented with acute dysphagia and retrosternal pain. He had a history of hiatal hernia with minimal gastroesophageal reflux. He had been treated with a granular laxative. On endoscopy, a mass was visualized. It was fragmented and partially extracted with the help of a polypectomy snare.⁶**
- **A 30-year-old female, without pathologic history, presented with complete aphagia and odynophagia. During the emergent endoscopic procedure, the gastroscope bumped into an occlusive granular bulk. It could not be removed by forceps manipulation but was eventually advanced with intravenous glucagon, which allowed the scope to progress into the stomach along with the granular laxative fragments.⁷**
- **A 91-year-old man developed an esophageal obstruction after ingesting a granular laxative (Normacol, Norgine Ltd, Middlesex) without water. This patient required laparotomy to remove the obstruction after rigid and flexible endoscopy attempts failed.⁸**

We found another published case report⁹ of psyllium granule aspiration in a 48-year-old female. This case involved accidental aspiration that did not appear to be associated with ingestion and/or esophageal obstruction with psyllium.

PERDIEM

Product information and labeling

Perdiem is available as natural bulk granular product plus vegetable laxative. This product contains 82% psyllium and 18% senna in a granular dosage form. It is also available without the senna. The directions for use indicate that the product be taken with at least eight ounces (a full glass) of cool water or other fluid. It indicates that taking the product without enough liquid may cause choking. The following steps for using Perdiem are also included on the bottle:

1. Moisten your mouth with a drink of water or any cool beverage.
2. Place a teaspoonful of granules on your tongue. If you prefer, take only a partial teaspoonful at a time.
3. Without chewing, wash granules down with water or any cool beverage.
4. Repeat steps 1-3 until the recommended dose has been swallowed. Be sure to drink at least 8 ounces of cool liquid.

Another section of the directions states that 1 to 2 rounded teaspoonsful one to two times daily should be placed in the mouth and swallowed with at least 8 ounces of cool liquid.

The bottle also contains the choking warning previously described in the introduction section. The bottle specifies that people with esophageal narrowing should not use bulk-forming agents.

Selection and Summary of Cases

AERS was searched on October 5, 2000 utilizing the higher level term (HLT) esophageal stenosis and obstruction and the preferred terms (PT) choking sensation, dysphagia, and sensation of foreign body linked to all identified psyllium products. This search resulted in the 73 unduplicated cases for Perdiem all from the US. Two of the cases were duplicates of the literature reports. The 78 AERS and literature cases are summarized below.

Demographic and other case information (N=78)

Age range: 28 to 85 years old, mean 69, median 70 (not reported - 27)
Gender: Females - 33, Males - 29, not reported - 16
Report year: 1980-8, 1981-2, 1982-2, 1983-10, 1984-11, 1985-15, 1986-4, 1987-4, 1988-7, 1989-3, 1990-1, 1993-3, 1994-1, 1996-1, 1999-2, 2000-4
Outcomes: Required medical intervention (59)
Died (1) Life-threatening (2)
Hosp/ER (29) Endoscopy (41)
Esophageal dilatation (2) Surgery (2)
Nasogastric tube (4) Pharmacological
intervention (7) Heimlich maneuver (1) Polypectomy
snare (1)

Resolved w/o intervention or

unknown (19)

All 78 cases of esophageal obstruction or blockage were temporally related to the use of Perdiem. Most cases involved elderly patients, however two occurred in 28-year-old males. One had a history of intermittent solid food dysphagia and the other reportedly had taken the product with insufficient water. There was only a slight difference with respect to gender. The majority of the cases were reported prior to the final monograph in 1994, with the highest number reported in 1985 possibly in response to the Dear Doctor letter. Since 1994, there have only been eight cases of esophageal obstruction, however it is worth mentioning that we have received four during the year 2000.

Possible risk factors were identified in 52% of the cases. Thirty patients had at least one risk factor, ten patients had two possible risk factors, and one patient may have had three factors that put them at risk for an esophageal obstruction or stenosis. These risk factors include hiatal hernia (13), CVA (3), Parkinson's disease (1), dysphagia (9), antral mass (1), Mallory Weiss Tear (1), AODM (1), and previous esophageal disorders (stricture (9), Schatzki ring (5), varices (1), narrowing (2), reflux (2), h/o esophageal obstruction (2), esophagitis, decreased motility (1), and spasms (2)). Of the eight cases reported since the warning was placed on the label, two reported one possible risk factor, two reported two possible risk factors, and four did not report risk factors. There were 37 cases with no reported or no apparent risk factors. One case specifically mentioned that esophageal endoscopy findings were normal.

The amount of Perdiem ingested was reported in only 32 of the 78 cases and ranged from 1 teaspoon to 2 tablespoons or it was reported as 6 to 24 grams. Only 27 cases made reference to the amount of water or fluid intake or appropriate use of the product. Nine of the 27 appeared to take the product appropriately, three reported that the product was taken as directed and six reported the product was taken with a full glass of water. Eighteen of the 27 cases may have taken Perdiem inappropriately. Two took Perdiem with four ounces of water, four took the product with "some" water, and 12 either took the product with insufficient or no water or they used the product in a manner that was inconsistent with the label. Of the eight cases reported since the warning was placed on the label, three reported using the product with water however none reported that the amount was insufficient.

In most cases, the obstruction appeared to resolve with medical intervention or resolved spontaneously. There was one reported death (FDA # 1747773). This case involved a female (age unknown) who required surgery to remove the obstruction. She died four months later. The case was not well

documented so it was unclear whether her death was due to postoperative complications.

In 59 cases, medical intervention was required to relieve the obstruction. In these cases, patients either sought medical attention via an emergency department or hospital admission, a primary physician, or gastroenterologist. This information was not always specified. The medical interventions included endoscopy or gastroscopy (41), esophageal dilatation (2), surgery (2), nasogastric tube (4), and/or pharmacological intervention (8) including use of enzymes, gas rocks [sic], glucagon, general anesthesia, mineral oil, and/or nitroglycerin. The remaining interventions include the Heimlich maneuver (1), polypectomy snare (1), and not specified (4). Of the two patients that required surgery, one was unrelated to the esophageal obstruction. His surgery was for an antral mass that was noted during the endoscopic procedure to relieve the obstruction. The other surgery was previously mentioned. In 19 individuals the obstruction spontaneously resolved or the case report did not indicate that medical intervention was required.

Several cases were noteworthy because the patients suffered sequelae as a result of the esophageal obstruction or the treatment required to dislodge the obstruction. These cases are described below.

Narrative summaries

FDA 3546987-0-00, direct/MFR 0303155A, IA, 2000

A 67-year-old female experienced esophageal obstruction after taking Perdiem according to the labeled instructions. According to the reporter (daughter-nurse), she put one teaspoonful on her tongue and washed it down with water. She began choking and was taken to the ER where an esophagram was performed. The physician attempted to advance the mass however was unsuccessful. She was then given "gas rocks", glucagon, and nitroglycerin to relax the esophageal sphincter. Following the administration of the medication, she experienced a fall in blood pressure requiring an IV fluid bolus and reverse Trendelenberg position. Within 10 minutes she was reportedly improved. Apparently she recovered however was still having pain and difficulty swallowing 10 days after the event.

FDA 718650, direct, KY, 1990

A 76-year-old female experienced an esophageal obstruction after approximately four doses of Perdiem. According to the report, the patient took a bolus of the "dry" Perdiem, followed by water. After several hours, she admitted herself to the ER. During an endoscopic procedure, she aspirated saliva. She went on to develop pneumonia and required hospitalization for five days. The reporter (pharmacist) stated that she had poor esophageal motility due to advanced age. No other esophageal abnormalities were

reported.

METAMUCIL

Product information and labeling

Metamucil (Procter & Gamble) is a bulk forming laxative containing psyllium husk. It is available as a powder (smooth or original texture and orange or regular flavored) or as wafers. The usual adult dose is one rounded teaspoon or tablespoon (depending on product version) one to three times per day. The labeled instructions indicate that the powder should be mixed with 8 ounces of liquid (e.g. cool water, fruit juice, or milk) and the wafers should be consumed with 8 ounces of liquid. Again, the choking warning is included on this product.

Selection and Summary of Cases

AERS was searched on October 5, 2000 utilizing the higher level term (HLT) esophageal stenosis and obstruction and the preferred terms (PT) choking sensation, dysphagia, and sensation of foreign body linked to all identified psyllium products. This search resulted in the 13 unduplicated cases for Metamucil products.

Demographic and other case information (N=13)

Age range: 59 to 82 years old, mean 71, median 70 (not reported - 2)
Gender: Females - 7, Males - 6
Year: 1981-2, 1988-1, 1989-3, 1996-1, 1997-4, 1998-1, 2000-1
Outcomes: Died (3), Hosp/ER (7), Resolved w/o intervention or unknown (3)
Location: US - 11, Canada - 2

There were 11 cases with one or more of the following reported events: choking, difficulty breathing, swelling of the throat, difficulty swallowing, and asphyxia. There were two cases of esophageal obstruction. All cases involved elderly patients with a mean of 71 years old. The outcomes include three patients that died, seven that required hospitalization, and three patients whose event resolved spontaneously. Two of the death cases were the result of asphyxiation and one died of laryngotracheal and left main bronchus obstruction.

In seven cases, hospitalization or emergency room treatment was required. The medical interventions included endoscopy (1), surgery (2), nasogastric tube (1), and/or pharmacological intervention such as IV fluids or treatment with an antihistamine (4). It is not clear in some of these cases whether the

event occurred as a result of the product swelling or the result of a possible allergic reaction to the product. Of the two patients that required surgery, one was due to an esophageal obstruction that resulted in perforation. The other patient reportedly required a surgical feeding tube because she was unable to swallow. That report was submitted by the patient and did not specify whether she had a swallowing disorder.

Possible risk factors were identified in three of the cases. These risk factors include esophageal stricture (1), concomitant administration of other medication (2), dysphagia (1), and possible alcohol or sedative use. In both cases involving esophageal obstruction, the patients had taken a concomitant medication at approximately the same time the Metamucil was taken.

The amount of Metamucil ingested was reported in only four cases and ranged from 1 teaspoon to 2 tablespoons. Seven cases made reference to the amount of water or other fluid intake that the Metamucil was mixed with. Three appeared to take the product appropriately. Four may have taken Metamucil inappropriately. One took Metamucil with four ounces of water and three took the product with less than the recommended amount of fluid.

Several cases were noteworthy and are described below.

Narrative summaries

FDA # 3578451-7-00, MFR # CIO00000127, KY, 2000

A 75-year-old schizophrenic male died after he ingested/aspirated Metamucil and contrast medium. According to the report, the nursing home patient swallowed 2 tablespoons of Metamucil stirred in 120 ml of water. He completely ingested the Metamucil along with several tablets within 30 seconds. He became agitated, started coughing, and experienced urinary incontinence within 4 minutes of the dose. The nursing staff found him unresponsive after he collapsed on the toilet. On autopsy, the bolus of congealed foreign material, which contained two partially dissolved tablets, formed a "molded cast fully obstructing the laryngotrachea and proximal esophagus, and subtotally obstructing the left mainstem bronchus. The cause of death was attributed to aspiration of the Metamucil and contrast medium. It is unclear when he ingested the contrast medium. This case report is in abstract form, although it is yet identified in my literature search.

FDA 2000321, MFR 172906, PA, 1996

A 65-year-old male developed an esophageal obstruction and perforation after he took an Aleve caplet along with his Metamucil. He had a past history of esophageal stricture. His physician noted on endoscopy the Aleve caplet stuck to the mucosal surface at the junction of the esophagus and the stomach, causing a perforation of his esophagus. Following this procedure,

he also experienced subcutaneous emphysema. He was treated with nasogastric suction, antibiotics, and hyperalimentation. The perforation eventually healed. He was hospitalized for a total of 15 days, five of which were spent in the intensive care unit.

AERS 648779, MFR COLL984229, MN, 1988

A female nursing home patient (age unknown) was given Metamucil in less than the recommended amount of water. The patient had a history of difficulty swallowing and was left alone when the patient took the product. When the attendant returned, the patient was choking and could not be revived.

AERS 128968, Canada, 1981

A 69-year-old male aspirated ingested Metamucil or Karacil, asphyxiated and died. His past medical history included obsessive-compulsive disorder, prior alcohol abuse, and diverticular disease. He was possibly on concomitant flurazepam. No other relevant details were provided.

SERUTAN

Product information

Serutan (Menley & James) is a bulk forming laxative containing psyllium. I was unable to locate this product in the current PDR. According to the USP DI®, Serutan is available as a powder and as toasted granules. The usual adult dose is one rounded teaspoon one to three times per day. The instructions indicate that the powder should be mixed with 240 mL of liquid and the granules should be sprinkled on food 1 to 3 times per day.

Selection and Summary of Cases

AERS was searched on October 5, 2000 utilizing the higher level term (HLT) esophageal stenosis and obstruction and the preferred terms (PT) choking sensation, dysphagia, and sensation of foreign body linked to all identified psyllium products. This search resulted in the seven unduplicated cases for Serutan.

Demographic and other case information (N=7)

Age range: 55 to 84 years old, mean 64, median 61 (not reported - 2)

Gender: Females - 3, Males - 4

Year: 1960-1, 1961-1, 1962-1, 1963-1, 1964-2, 1984-1

Outcomes: Hospitalization (7)

Location: US - 7

In general these cases were poorly documented. Also of note, they all occurred much earlier than when they were reported, with the earliest occurring in 1960. All reports were submitted in 1990 and may have been submitted by SmithKline Beecham.

There were three cases of choking and/or difficulty swallowing and four cases of esophageal obstruction. All cases involved older patients with a mean of 64 years old. All seven patients were reportedly hospitalized. One patient required surgery to remove the obstruction. One patient had a reported history of esophageal distress.

The amount of Serutan ingested was reported in only four cases and ranged from 1 to 2 teaspoonfuls. Two appeared to take the Serutan appropriately, four may have taken it inappropriately, and one case did not provide that information.

DISCUSSION/ CONCLUSION

We reviewed 98 cases of esophageal obstruction and related events associated with the use of psyllium products. The three products involved include Perdiem-78, Metamucil-13, and Serutan-7. We were unable to locate any reports for other OTC psyllium products.

In general these events occurred in elderly patients many that may have had risk factors for these events. The cases involving Perdiem differed somewhat from the Metamucil cases. To begin with, practically all Perdiem cases involved esophageal obstruction. In many cases the mass or bezoar was visualized and in some cases described. Metamucil cases included esophageal obstruction (2) as well as choking-related events (11). Some of these may have been allergic reactions and others involved aspiration of Metamucil.

Approximately half of the Perdiem cases were related to the use of the product in patients that may have had one or more risk factors, primarily esophageal disorders. Of the two Metamucil obstruction cases, one had a possible risk factor but both were possibly due to administration of another drug product at the same time the Metamucil was given.

Information regarding appropriate or inappropriate use of these products was most often not reported. Specifically, it is not clear whether the obstruction was the result of inappropriate use or insufficient fluid or water intake. There are at least nine Perdiem cases that specified that the product was used appropriately, six of which also did not pinpoint risk factors.

Based on our review of the cases, esophageal obstruction with Perdiem continues to occur despite the increased warnings regarding use of the products with adequate fluid intake. For this reason, it would seem

reasonable that the sponsor be requested to reformulate Perdiem. Esophageal obstruction occurred with Metamucil when it was given concomitantly with other medications. We recommend that Metamucil powder be relabeled to warn the consumer against taking this product at the same point in time as other medications.

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Signed 11-17-00

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