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2012 JUN -6 A 10:37

June 3, 2012

U.S. Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm 1061
Rockville, Maryland 20852

Citizen Petition to Investigate Polyethylene Glycol 3350 Product Safety for Use with Pediatric Patients

Includes 32 page petition and 66 attachments including parent statements.

The undersigned submits this petition under Title 21, Food and Drugs Chapter I, Department of Health and Human Services Subchapter A, General, Section 10.30 Citizen Petition to request the Commissioner of Food and Drugs to investigate the safety of polyethylene glycol 3350, its metabolites (and any possible contaminants) for use with pediatric patients. We petition the Commissioner to take the following actions to protect the health and safety of children as soon as possible.

A. Action Requested

This petition requests that the Commissioner of Food and Drugs take administrative action in the form of:

1. An immediate recall of PEG 3350 laxatives for addition of a black box warning against use in children and warning of potential adverse events associated with PEG 3350 laxative products. Adverse events reported in the FDA Adverse Event Reporting System include, but are not limited to: gastrointestinal, renal, urological, hematological, neurological, neuropsychiatric, dermatological, and at least 3 child fatalities. Adverse events are also outlined by the FDA Drug Safety Oversight Board in its June 18, 2009 Meeting Public Summary (see page 3).

2. Investigation of the relationship between ethylene glycol toxicity symptoms, diethylene glycol toxicity symptoms and the polyethylene glycol adverse events reported by parents of children taking PEG 3350.

3. Review and disclosure all results of completed clinical trials on PEG 3350 products that have not been published.

4. Investigation of the long term effects of short term polyethylene glycol 3350 use on human health.

5. Investigation of the effects of long term polyethylene glycol 3350 use on human health.

6. Investigation of the long term effects of short term and long term use of polyethylene glycol 3350 products in pediatric patients in particular.

7. Investigation of the effects of polyethylene glycol 3350 use in treating chronic constipation.

FDA-2012-P-0566

CP

2012-454

B. Statement of Grounds

Polyethylene glycols are petroleum based compounds used as osmotic laxatives due to their ability to pull water from the body and into the bowel.

In 2004, Mrs. Jeanie Ward, a parent whose child was experiencing adverse events while taking a prescribed polyethylene glycol laxative, petitioned the Food and Drug Administration to investigate the effects of the drug on children. Jeanie Ward and another parent, Mary Wetherby started an online support group for parents who felt their children had been harmed by Miralax and other PEG products, the Miralax Yahoo Group at http://health.groups.yahoo.com/group/miralax/, now over 1637 members strong and growing daily.

In the fall of 2011, Empire State Consumer Project learned of the Miralax Yahoo Group and began researching the complaints posted by group members, many of which have been submitted to the FDA over the past seven years. Much of the information presented in this petition was gathered by the parents whose children have suffered adverse while taking PEG 3350 and are searching for answers.

Based on its own findings and the soaring number of adverse events reported to the Food and Drug Administration, we are asking the FDA to reopen its investigation of polyethylene glycol products in pediatric patients, as the safety of PEG 3350 use in children has not been established by the FDA and, at its Drug Safety Oversight Board meeting in 2009, numerous serious safety concerns were outlined by the Board (see following page for Public Summary).

As of March 2012, the FDA Adverse Event Reporting System showed 2257 reported adverse events related (in any way) to PEG products – up from 7 in 2001. Included in the adverse events reported are serious kidney, urinary, bowel, blood, skin, and neuropsychiatric symptoms - and at least 3 children's deaths. As of August 15, 2011, FDA states on its website that polyethylene glycol oral laxative (various trade names) are related to "Neuropsychiatric Events" (under Potential Signal of Serious Risk / New Information) and goes on to state that "No regulatory action is needed at this time."

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm161063.htm

Although some of this report contains information on the products Miralax, Golytely, and Clearlax, we urge the FDA to study the active ingredient Polyethylene Glycol in any medical product that is being prescribed to children in the United States or sold by US companies for overseas use.

History of Adverse Events Related to Polyethylene Glycol on File with FDA

7	Adverse events, November 2000
54	Adverse events, April 2001
89	Adverse events, March 2002
161	Adverse events, October 2003
238	Adverse events, September 2004
447	Adverse events, January 2006
665	Adverse events, April 2007
869	Adverse events, March 2008
1,014	Adverse events, October 2009
1,966	Adverse events, June 2011
2,257	Adverse events, March 2012

B. Statement of Grounds, Continued

Following is the Public Summary from the FDA Drug Safety Oversight Board that reviewed the use of polyethylene glycol products for pediatric patients in 2009. It outlines serious safety concerns, but no action was taken regarding the use of polyethylene glycol products as result of this meeting.

Drug Safety Oversight Board Meeting, June 18, 2009

Public Summary

The Executive Director updated the Board on risk communications [Public Health Advisories (PHAs), Early Communications about Ongoing Safety Reviews (ECs), and Information for Healthcare Professionals (HCP)] posted and in development since the May 21, 2009 meeting.

The Drug Safety Oversight Board discussed reports of **metabolic acidosis, metabolic acidosis with increased anion gap, and neuropsychiatric adverse events in children** using polyethylene glycol (PEG) products. Metabolic acidosis is a disturbance in the body's acid-base balance and causes too much acid in the blood. In some situations, metabolic acidosis can be a mild, chronic condition; however, it **may lead to shock or death in severe cases. Neuropsychiatric adverse events may include seizures, tremors, tics, headache, anxiety, lethargy, sedation, aggression, rages, obsessive-compulsive behaviors including repetitive chewing and sucking, paranoia and mood swings.**

PEG is a laxative that increases the amount of water in the intestinal tract to stimulate bowel movements. There are currently 19 PEG products, prescription and over-the-counter (OTC), in the US approved for use as either as a bowel preparation prior to colonoscopy or for the treatment of constipation. All products approved for use prior to colonoscopy are prescription products with one product approved for use in children 6 months and older. There is only one PEG product available over-the-counter and it is indicated for short term use (up to 7 days) in adults and children 17 years of age or older with occasional constipation. The Constipation Guideline Committee of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition has formulated PEG product guidelines for long-term use in the management of pediatric constipation; however, **this indication is not FDA approved.**

The Board discussed whether the adverse event reports constituted a safety signal and what if any action should be taken for the prescription and over-the-counter preparations used. The Board was assisted by Andrea Gropman, MD who served as the Board's guest expert in pediatric neurology.

Dr. Andrea Gropman is a child neurologist and clinical geneticist at the National Institutes of Neurological Disorders and Stroke at the National Institutes of Health and the Children's National Medical Center in Washington, DC.

Some of the issues highlighted by the Board are:

1. PEG is a long-chain polymer of ethylene oxide commercially available in molecular weights of 300 g/mole to 10,000,000 g/mole. Many products contain an average molecular weight of 3350 g/mole and thus are given the name PEG-3350. PEG-3350 products exist in a stable powder form. Approved products instruct patients to dissolve the PEG-3350 powder in a liquid and use immediately. The approved products have been tested under these conditions and are stable. **It is unknown if prolonged duration in solution would change the chemical properties of PEG-3350, and what the actual content of ethylene glycol or diethylene glycol or other low molecular weight PEG would be under such conditions**.
2. PEG products that are available over-the-counter can be used without medical oversight.
3. There is a perception that PEG is safe because it is minimally absorbed from the stomach and intestines. However, little is known about whether absorption in children differs from adults, especially in children who are constipated, have underlying intestinal disease, or are very young.
4. Children are receiving adult doses of PEG in some cases.
5. Children may be more susceptible to variations in PEG product quality.
6. Effects of large doses of PEG given over a long duration (e.g weeks or longer) is not known.

B. Statement of Grounds, Continued

Letter from Nexgen, a manufacturer of Clearlax, a PEG 3350 product, warning against use in children...

Nexgen
Permalink

This letter is in response to your complaint as listed above. All production and quality records indicate that the manufacturing process was followed per the established procedures. In addition, quality control testing confirmed that the product met USP NF requirements for Polyethylene Glycol.

This product is tested and approved for use by adults only. Labeling clearly states that pediatric safety and effectiveness has not been evaluated for the product and there is no recommended pediatric dose. We do not recommend or endorse this off-label use and we cannot predict the possible problems children may experience using the product.

Thank you for bringing this incident to our attention and I want to assure you of our ongoing commitment to product quality and to our customers. Nexgen takes each and every product observation or issue that has been brought to our attention very seriously and we make every effort to continually improve our products, processes and service. Please feel free to contact me anytime if you have any additional questions or if I can be of further assistance.

Sincerely,

Elaine Tanabe
Quality Assurance

File Name: Nexgen
Posted: Dec 6, 2009
Resolution: 480x332
Size: 48KB

B. Statement of Grounds, Continued

Doctors Concerned about Polyethylene Glycol Toxicity

In Golytely Solution for Colonoscopy Preparation, a 1984 letter to the editor of Gastrointestinal Endoscopy, Drs. Joseph DiPiro, PharmD, Talmadge A. Bowden, Jr., MD, John F. Sisley, MD, and Frances J. Tedesco, MD of Gastrointestinal Surgery and Gastroenterology at Medical College at Georgia say,

"Our concern is the potential toxicity of polyethylene glycol which is a major ingredient of the Golytely solutions (polyethylene glycol 3350, 59 g/liter). The oral toxicity has been studied in animals with reported LD, for guinea pig, rat and rabbit to be 50.9, 59 and 76 g/kg respectively, and...oral dose over 20 g/kg in rats "cloudy swelling" was noted in kidney and liver tissue. Union Carbide, the manufacturer of polyethylene glycol 3350, reports no deaths in the guinea pig and rat with similar doses as above, but did observe uremic deaths in some rabbits given 50 mg/kg orally.

Polyethylene glycol is usually regarded as being non-absorbed. However, data are available which indicate that this is not the case. Fecal recovery of polyethylene glycol 3350 has been studied after oral ingestion and been found to range from 96.3 to 100.1%. Soergel found that after a 15-g oral dose 96.9% +/- 2.8% was recovered in the effluent of six ileostomy patients. In rats that received a 10-mg oral does of C-labeled polyethylene glycol 3350 4.1% was recovered in the urine. Patients ingesting 4 liters of a Golytely solution would receive an oral dose of about 240 g of polyethylene glycol which could result in a potential systemic dose of 9.6 g.

Concern for the human toxicity of polyethylene glycol and other glycols has been raised. The carcinogenic potential of these agents has been addressed. The FDA Drug Bulletin describes adverse effects in burn patients after absorption of polyethylene glycol from topical preparations which can also result in toxicity similar to ethylene glycol ingestion.

...we feel that the data on polyethylene glycol...and toxicity in humans are insufficient, and we...have studies in progress to clarify this. This information would allow a better assessment of the risks of using these solutions."

B. Statement of Grounds, Continued

From Jeanie Ward, Co-Founder of the Miralax Yahoo Group

Dear FDA,

My name is Jeanie Ward and I've spent a decade researching the effects of polyethylene glycol in children because my daughter had a residual adverse reaction to this medication. I petitioned the FDA to take a look at something that far exceeds a black box warning change. This chemical is poisoning our children, many children have died, and it needs an immediate, nationwide recall to all physicians prescribing this drug to children.

After I petitioned the FDA regarding this matter, they held a Drug Oversight Board Meeting 8 years later, with no official decision. Polyethylene Glycol was approved for adults with the theory and that it was poorly absorbed. Once approved for adults, prescribing spread like wild fire and physicians across the globe are prescribing this drug against the manufacturer's advice to children as young as 2 months old.

What does happen when it's absorbed? It was approved with the belief that it was supposed to be poorly absorbed, so if they were correct, we shouldn't be seeing any adverse reactions to this medication, but we are, by the thousands, and many children are suffering the consequences of this unfortunate situation.

The chemical structure of polyethylene glycol is similar to ethylene glycol, but applying for FDA approval, the experts submitted evidence showing that they are different and PEG is poorly absorbed. How could we be seeing identical symptoms to ethylene glycol if this assumption was correct? These children are dying, exhibiting renal failure and a lengthy list of symptoms that are identical to ethylene glycol poisoning, so we suspect more is being absorbed than the original studies have shown.

Physicians are prescribing even though the manufacturer states for use for "occasional constipation" and many of these children are being prescribed this medication for chronic constipation, which upon x-ray clearly shows a bowel obstruction, leaving the medication nowhere to go, being absorbed by the intestinal tract. Enclosed are the families' testimonies we would like you to review. The manufacturer also states not to use more than 7 days - physicians are prescribing for years without knowing the long term effects.

In 2001, I petitioned the FDA regarding this matter and in 2002, a woman contacted me from halfway across the United States who was searching the FDA data base for information regarding this issue, due to her son's adverse reaction. She called me and we decided to put a Miralax group together as a support group and see if others were experiencing the same symptoms. Our group is titled, Miralax@yahoogroups.com and consists of 1637 members with hundreds of testimonies to back up our research.
http://health.groups.yahoo.com/group/miralax/

Someone needs to investigate the effects of this drug on children and alert medical professionals. The neurological behavior changes alone, the deaths, and the long list of symptoms reported are a clear indication that the medication is harming these children, and it needs to be investigated immediately!

Parents are pleading with their physicians for answers, but the physicians stand behind a protocol that was intended for adults, leaving these children with no acknowledgement of the permanent damage that this drug did to them. Who is going to acknowledge what happened to these children? How can they help treat these children with permanent conditions when they are unaware of the side effects and no one is monitoring the adverse reactions or warning physicians what is happening to OUR children?! How can we prevent more children from being harmed if we don't take action NOW? Every day we wait more children are being hurt.

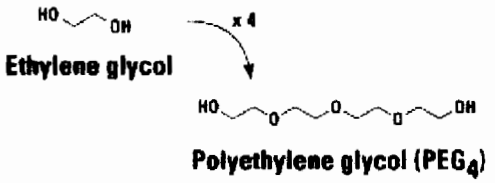
Thank you,
Jeanie Ward dreamjeanie@att.net 815-322-3771

B. Statement of Grounds, Continued

What is Polyethylene Glycol?

"**Polyethylene glycol (PEG)** is a polyether compound with many applications from industrial manufacturing to medicine. It has been known as **polyethylene oxide (PEO)** or **polyoxyethylene (POE)**, depending on its molecular weight, and under the trade name **Carbowax**." http://www.4spe.org/plastics-encyclopedia/polyethylene-glycol

PEG is the common abbreviation for polyethylene glycol – or, more properly, poly (ethylene glycol) – which refers to a chemical compound composed of repeating ethylene glycol units:



http://www.piercenet.com/browse.cfm?fldID=12D97D8D-5056-8A76-4E95-9EA0D0B54BDB

Dr. David Suzuki, Noted Geneticist on PEG

Noted geneticist, Dr. David Suzuki, in his Suzuki Foundation article, PEG Compounds and Their Contaminants explains the health and environmental hazards of polyethylene glycol...

Use in Cosmetics

PEGs (polyethylene glycols) are petroleum-based compounds that are widely used in cosmetics as thickeners, solvents, softeners, and moisture-carriers. PEGs are commonly used as cosmetic cream bases. They are also used in pharmaceuticals as laxatives.

Health and Environmental Hazards

Depending on manufacturing processes, PEGs may be contaminated with measurable amounts of ethylene oxide and 1,4-dioxane. [i] The International Agency for Research on Cancer classifies ethylene oxide as a known human carcinogen and 1,4-dioxane as a possible human carcinogen. Ethylene oxide can also harm the nervous system [ii] and the California Environmental Protection Agency has classified it as a developmental toxicant based on evidence that it may interfere with human development. [iii] 1,4-dioxane is also persistent. In other words, it doesn't easily degrade and can remain in the environment long after it is rinsed down the shower drain. 1,4-dioxane can be removed from cosmetics during the manufacturing process by vacuum stripping, but there is no easy way for consumers to know whether products containing PEGs have undergone this process. [iv] In a study of personal care products marketed as "natural" or "organic" (uncertified), U.S. researchers found 1,4-dioxane as a contaminant in 46 of 100 products analyzed. [v]

B. Statement of Grounds, Continued

Dr. David Suzuki, Noted Geneticist on PEG, Continued

While carcinogenic contaminants are the primary concern, PEG compounds themselves show some evidence of genotoxicity [vi,vii] and if used on broken skin can cause irritation and systemic toxicity. [viii] The industry panel that reviews the safety of cosmetics ingredients concluded that some PEG compounds are not safe for use on damaged skin (although the assessment generally approved of the use of these chemicals in cosmetics). [ix] Also, PEG functions as a "penetration enhancer" increasing the permeability of the skin to allow greater absorption of the product — including harmful ingredients. [x]

http://www.davidsuzuki.org/issues/health/science/toxics/chemicals-in-your-cosmetics---peg-compounds-and-their-contaminants/

Polyethylene Glycol 3350 Material Safety Data Sheet

We understand that Material Safety Data Sheets can be used to describe the industrial form of a chemical used to make an end product, yet Miralax is made of 100% Polyethylene Glycol 3350, with no additional ingredients added. The warnings that Polyethylene Glycol 3350 is a flammable, explosive skin irritant, not to be ingested or inhaled, for which safety goggles, lab coat, and dust respirator must be worn while handling are concerning to parents, especially those who have experienced adverse events. Little is known about 'serious ingestion,' carcinogenic effects, or developmental toxicity. Parents are interested in knowing what manufacturing processes PEG 3350 goes through to make it 'safe' for human consumption.

http://www.sciencelab.com/msds.php?msdsId=9926625

Toxicity of Polyethylene Glycol in Animals

Exposure to polyethylene glycol resulted in embryotoxicity in animals...

http://www.mindfully.org/Plastic/Polymers/Polyethylene-Glycols-PEGs.htm

B. Statement of Grounds, Continued

Miralax Intended Use

According to its product label, Miralax is intended for short term use in adults to treat occasional constipation.

The original Miralax product label warned against use in children. The current label directs "Children 16 years of age or under: consult a doctor," even though FDA has not approved this drug for pediatric use.

http://www.miralax.com/miralax/hcp/product-information.jspa#miralax-label

Questions...

1. Are pediatricians following the guidelines created by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, regardless that these guidelines are not approved by the FDA? (See preceding FDA Drug Safety Oversight Board Meeting Public Summary on page 3).

2. Is this off-label use what prompted the label change suggesting pediatricians should be consulted for pediatric dosing?

3. Does this change in off-label marketing constitute new marketing of a product for use in children, which would require the manufacturer to apply to the FDA for approval?

B. Statement of Grounds, Continued

Miralax Off-Label Use

Per FDA's Off-Label Use Guidelines, "If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects."

Miralax is being used in violation of FDA Off-Label Use guidelines.

1. **Prescribed to children in adult doses** – In 1999, doctors around the US began prescribing Miralax to children. Of the over 1637 members of the Miralax Yahoo Group (membership increases daily), most are members whose children were prescribed Miralax by their doctor, some as young as 2 months old (yet Miralax is not recommended for use by pregnant women). No testing has been done to prove that Miralax is safe for use in children. Children are being prescribed adult doses and multiple adult doses per day.

2. **Prescribed for long term use** – Many of the Miralax group parents have had their children prescribed Miralax for longer than the 7 day period recommended on the product label - some of them for years. In addition, label directions say to use Miralax just once per day. Doctors are prescribing Miralax to be taken multiple times daily. No research has been done on the effects of long term Miralax use. High doses of polyethylene glycol can result in hyponatremia, low blood sodium, which causes the body's cells to swell and can be fatal. Prepubescent children are at higher risk.
   http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1125242/

   Regarding lasting effectiveness, this study showed a majority of people who used PEG 3350 required additional constipation treatment interventions after 30 days of PEG 3350 use.
   http://www.ncbi.nlm.nih.gov/pubmed/16000928

   Long term use of polyethylene glycol laxatives can cause dependence on laxatives. Extreme caution is recommended for use in children.
   http://www.drugs.com/cdi/miralax-powder-for-oral-solution.html

3. **Prescribed for chronic constipation** – Many of the Miralax group parents have had their children prescribed Miralax for chronic, rather than occasional constipation. No research has been done on the effects of Miralax on patients with chronic constipation.

4. **Adverse events records under-reported** – According to parents, most prescribing physicians are not reporting to the FDA the polyethylene glycol adverse effects parents have reported to them. Some parents tell of being treated disrespectfully by doctors when bringing up the topic of adverse events they say their children have experienced while taking polyethylene glycol products. Doctors are not indicating to parents any knowledge of the FDA Drug Safety Oversight Board Meeting of June 2009 and its findings. This causes parents to wonder what communication is made to ensure that doctors read the Public Summary issued by the FDA Drug Safety Oversight Board, which warns of potential dangers associated with PEG use in children.

B. Statement of Grounds, Continued

Miralax Off-Label Use, Continued

Deaths Not Reported

In the study Fatal Dysnatremia Caused by Elective Colonoscopy, three patients who died after being administered a PEG colon cleanse. The deaths were not reported by the manufacturer, Braintree Laboratories. Seizures in patients with no prior history of seizures were also not reported. Braintree did not agree to comply with recommendations to list these events in its Adverse Events labeling.

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021551s000_HalfLytely%20Tabs_medr.PDF

5. **Bowel obstruction not ruled-out** – Miralax is not to be taken if a bowel obstruction is present. According to parents on the Miralax Yahoo Group, doctors are not always testing for bowel obstruction before prescribing Miralax or, in many cases, are not testing for other organic causes of constipation. In fact, parents feel that hard, un-passed stool alone (some shown on x-ray) is an obstruction, which leads some doctors to increase dosage in an attempt to unblock the bowel.

   The marketing materials created by Braintree Labs states, "Patients with constipation should be evaluated for bowel obstruction or metabolic disorder."

   One child of a parent on the Miralax Yahoo Group who almost died while on Miralax had his colon pronounced 'abnormal and dead' along with part of his small intestine. They were removed to save his life. Cell death can be *caused* by polyethylene glycol (as in the case of a woman who suffered PEG related tubular necrosis). http://www.ntuh.gov.tw/PMR/Lists/List14/Attachments/164/10253009-200903-37-1-45-50-a.pdf).

   Miralax promotional materials claim "No Cramping, No Bloating, No Gas," yet advises to stop use if cramping, bloating, or abdominal pain worsen while taking the product, as these may be signs of a serious condition. http://www.miralax.com/pdf/MiraLAX_ProductLabel.pdf

6. **Sound medical evidence lacking** – According to the FDA Drug Safety Oversight Board, "There is a perception that PEG is safe because it is minimally absorbed from the stomach and intestines. However, little is known about whether absorption in children differs from adults, especially in children who are constipated, have underlying intestinal disease, or are very young. Effects of large doses of PEG given over a long duration (e.g. weeks or longer) is not known."

   What does this say about prolonged duration in the human body?

   Polyethylene glycol solutions are to be discarded if not used within 48 hours of being mixed. **Often, children are prescribed repeated doses of PEG to unblock the bowel, leading parents to wonder about the effect of PEG sitting in the intestines for days while waiting for stool to pass.**

   Polyethylene Glycol is a polymer of ethylene oxide. Ethylene oxide is found in the production of solvents, antifreeze, textiles, detergents, adhesives, polyurethane foam, and pharmaceuticals. http://www.chemistrydaily.com/chemistry/Polyethylene_glycol. Some scientific literature makes a major distinction between the properties of polyethylene glycol and ethylene glycol, antifreeze, but parents are concerned.

   Parents want to know: Why are PEG adverse events their children are experiencing similar to those related to ingestion of ethylene glycol?

B. Statement of Grounds, Continued

History

Miralax, manufactured by MSD Consumer Care, Inc., a division of Merck & Co., Inc., is one of a group of products made of PEG 3350, polyethylene glycol. When it was created by Braintree Laboratories in 1999, Miralax was a prescription drug. In 2009 Miralax, then owned by Schering-Plough Corporation (which later merged with Merck), was approved as an over-the-counter medication.

FDA False Claims Warnings...

In 1999 the FDA issued a warning letter to Braintree Laboratories, Inc., the creator of Miralax for failing to list any risk warnings with its product literature...

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCcompanies/UCM166151.pdf

In a 2001 warning letter from the FDA to Braintree Laboratories, the FDA states that Miralax was NOT found to be superior to fiber in treating constipation. The manufacturer was also warned of a number of other unsubstantiated claims and that the drug's warnings, contraindications, precautions and adverse reactions appeared in a micro-type paragraph at the bottom of the page, in violation of FDA labeling requirements...

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM166481.pdf

To this day, Miralax ads claim, "No Gas, No Bloating, No Cramping," all of which are side effects of the drug.

In 2008, at FDA's request, another type of laxative products, Fleet Phospho-Soda oral sodium phosphate bowel cleanse and E-Z Prep Bowel Cleansing System were withdrawn from the market after the FDA warned of the risk of kidney damage associated with sodium phosphate laxative products. Other prescription sodium phosphate products added an FDA required warning box telling consumers of the potential for kidney damage. When sodium phosphate bowel cleanse products were called into question, PEG products were considered by some to be a safer alternative.

This article states that sodium phosphate products were seen to be more effective than PEG products (and the data that follow in this petition cast serious doubt on the safety of PEG products for pediatric patients).

(http://journals.lww.com/jpgn/Abstract/1996/12000/Comparison_of_Oral_Sodium_Phosphate_to.13.aspx)

B. Statement of Grounds, Continued

Proven Risks in Off-label Prescribing

Physician Error Rampant in Off-label Survey

Parents are confused about off-label use of drugs, especially those prescribed to children. They trust their doctors to prescribe treatments that are proven to be safe for children and, after experiencing adverse events, they are shocked to learn that the drug their child has ingested, sometimes in larger than adult doses over long periods of time, is not approved for use in children at all.

Apparently, parents and other consumers are not the only ones confused about off-label prescribing. According to the New York Times, in a 2009 study in Phamacoepidemiology and Drug Safety, a survey of physicians found that many might not even know when they are prescribing off-label. **"Of some 600 doctors surveyed, the average physician identified the FDA approval status correctly for only about half the drugs on a list provided by the researchers.** Nearly one in five who prescribed Seroqquel (quetiapine) in the previous year thought it was approved for patients with dementia and agitation, even though it was never approved for this use and even carried a 'black box' warning that it was dangerous for elderly patients with dementia. And one in three doctors who used lorazepam (often marketed at Ativan) to treat chronic anxiety thought it had been approved for this use; in fact, the FDA warning advises against using it for this purpose. The study's senior author, Dr. G. Caleb Alexander, assistant professor of medicine at the University of Chicago, said a concern was that off-label uses often did not have the same level of scientific scrutiny as FDA-approved uses."

http://www.nytimes.com/2009/08/25/health/research/25disp.html

In 2006, Dr. Dean R. Focht outlined highlights of the North American Society for Pediatric Gastroenterology, Hepatology protocol, which includes a 1.5 g/kg of body weight cleanout dose, then 1 g/kg daily maintenance dosage along with behavior recommendations including regular toilet sitting (three times per day) and sticker charts to improve compliance. He claims a 57% "cure" rate with the protocol. Dr. Focht was shocked at doctor lack of awareness, stating that "Some pediatricians thought Miralax could only be used for 2 weeks," while the product label clearly says not to use for more than 7 days.

http://findarticles.com/p/articles/mi_hb4384/is_12_40/ai_n29314476/

If doctors are not aware that they are prescribing Miralax off-label, or they are aware and are prescribing it regardless, they need to be educated about the adverse events that have been reported to the FDA.

B. Statement of Grounds, Continued

Proven Risks in Off-Label Prescribing, Continued

Off-label Prescribing in Neonatal Intensive Care Units

According to this article in the 2005 FDA Science Forum, **up to 90% of NICU patients are exposed to drugs that are either unlabeled or used in an off-label manner, including polyethylene glycol.**

"A New Face on an Old Problem: Excipient Exposure in the Neonatal Intensive Care Unit S. K. McCune, S. Y. Buckman, W. J. Rodriguez, OCTAP, CDER, FDA, Rockville, MD

In 1937, sulfanilamide was compounded with diethylene glycol to improve solubility; 107 patients, many of them children, died due to diethylene glycol toxicity. In 1981, the neonatal gasping syndrome secondary to benzyl alcohol toxicity was reported. Extremely low birth weight (ELBW) infants receive significant numbers of medications, putting them at risk for acute and chronic exposure to single or multiple excipients.

A literature review of common excipients led to a focused examination of drug labels for some commonly used drugs in the neonatal intensive care unit (NICU). Also, accepted standards of excipient exposure were examined. Up to 90% of NICU patients are exposed to drugs that are either unlabeled or used in an off-label manner. This study does not endorse the off-label use of these drugs but only examines the potential exposure to excipients during a NICU admission.

Benzyl alcohol, propylene glycol, **polyethylene glycol**, sodium benzoate, and polysorbate are excipients found in drugs commonly used in the NICU. Aminophylline, Vitamin K, lorazepam, bumetanide, dexamethasone, diazepam, doxapram, pancuronium, phenobarbital, hydrocortisone, methylprednisolone, succinylcholine, enalapril, midazolam and Vitamin E preparations contain benzyl alcohol. Lorazepam, phenytoin, digoxin, MVI-12®, phenobarbital, and diazepam contain propylene glycol. Lorazepam contains polyethylene glycol, diazepam contains sodium benzoate, and MVI® pediatric contains polysorbate. Excipient concentrations and potential exposure will be discussed.

It will be important to document individual neonatal excipient exposures compared to known thresholds. Future trials need to determine the metabolism of excipients in ELBW infants and the potential long-term effects of chronic excipient exposure."

B. Statement of Grounds, Continued

Excretion, Permeability, Metabolism

Excretion

Again, it is unclear how much polyethylene glycol is eliminated by the body. This article states that, in constipated patients, Miralax recovery is incomplete and highly variable...

http://www.druglib.com/druginfo/miralax/description_pharmacology/

According to this study, up to 4% of PEG 6000, a larger molecule, is metabolized in humans. Parents conclude that, if a larger molecule is metabolized, it stands to reason that PEG 3350 may be metabolized.

http://dmd.aspetjournals.org/content/35/1/9/T1.expansion.html

Permeability

Although one study was found to the contrary, parents feel that, as their intestines are more porous, children with Leaky Gut Syndrome who take PEG 3350 for chronic constipation may be absorbing more than the average person.

People with Crohn's Disease, another condition that causes increased permeability, absorb more PEG 400 than those with healthy intestines. Although PEG 400 is a smaller molecule than PEG 3350, this points to the increased permeability in people with compromised intestines. http://www.annals.org/content/105/6/883.short

In patients with certain viruses, intestinal permeability was increased, allowing more PEG to pass through the intestinal wall. http://www.ncbi.nlm.nih.gov/pubmed/2693681.

Use of polyethylene glycol is not recommended for breastfeeding women because it is not known whether PEG passes into breast milk. This leads parents to wonder all the more whether it permeates compromised intestines.

Metabolism

FDA's guidance document on food and color additives offers a layperson's guide to absorption, metabolism, distribution, and elimination criteria for food products, which mirrors parent questions on PEG metabolism...

- "Does the product or its metabolites alter or interfere with absorption, metabolism, or excretion of normal nutrients or metabolic intermediates?
- Does the product or its metabolites alter the action of commonly used drugs?
- Is the product absorbed, metabolized, distributed, stored or excreted differently in man than in test animals?
- Does the product or its metabolites accumulate in tissues, and what are the toxicological consequences if there is accumulation?
- If the product is poorly absorbed, does the high concentration in the gut affect gut morphology, physiology, or biochemistry? Are any changes in the gut morphology or biochemistry associated with the development of neoplasms of the gut?
- Does the product alter the composition or nature of the gut flora? If it does, what are the toxicological consequences of the changes?"

B. Statement of Grounds, Continued

Cell Death

The following article published in 2006 is exploring the effect of oral polyethylene glycol in increasing the rate of apoptosis (cell death) of the intestinal epithelium. This change is seen as a benefit to reducing colon cancer, and the effect is apparently rapid. This is how the study described this effect of PEG on the mucosa:

"Taken together, these facts suggest that PEG has an abrasive effect on the mucosa. How could abrasion be protective? Although it is highly controversial, the elimination of cells from the top of crypts might be enough to stop carcinogenesis, by preventing the top-down movement of transformed cells (38). This would explain why the inhibition was reversible in part when treatment was discontinued (6). Similarly, chemical peeling with PEG and salicylic acid strikingly suppresses skin tumor development in mice (39). "
http://www.ncbi. nlm.nih.gov/ pmc/articles/ PMC2643349/

Adverse Events

Following are adverse events posted by Yahoo Group members whose children have been prescribed polyethylene glycol products and events reported to the FDA Adverse Event Reporting System.

Kidney/Urinary/Blood Symptoms

Many parents on the Miralax Yahoo Group report kidney/urinary and related blood symptoms. .

Oxylates in Urine

A medical journal explains the connection...

According to one study, "The presence of metabolic acidosis and urinary calcium oxylate crystals were noted, so PEG-related oliguric acute tubular necrosis was suspected. **The above symptoms were similar to those seen with ethylene glycol intoxication. We conclude that bowel preparation with PEG lavage solution may be associated with severe renal complications, and that physicians should be aware of possible adverse effects when administering the agent.** (Tw J Phys Med Rehabil 2 "
http://www.ntuh.gov.tw/PMR/Lists/List14/Attachments/164/10253009-200903-37-1-45-50-a.pdf

Oxalates can also be induced using ethylene glyclol, a chemical related to polyethylene glycol.

http://www.biomedcentral.com/1471-2490/7/18)

Metabolic acidosis

Metabolic acidosis is too much acid in the body, or not removed by the kidneys. (This condition can also be caused by ethylene glycol poisoning).

http://health.nytimes.com/health/guides/disease/metabolic-acidosis/overview.html

Dysnatremia (Hyponatremia /Hypernatremia)

Dysnatremia is an electrolyte abnormality caused by fluid imbalance in the body. The following article explains how dysnatremia can lead to brain damage in children...

http://www.springerlink.com/content/p673624q47368117/

Patients with hyponatremia may present severe neurologic dysfunction. Parents on the Miralax Yahoo group have not been warned of this potential side effect and product labels do not include it as a side effect.

http://emedicine.medscape.com/article/767624-treatment

B. Statement of Grounds, Continued

Adverse Events, Continued

Dysnatremia (Hyponatremia /Hypernatremia), Continued

The following article published in the British Medical Journal describes the way in which PEG products can cause this dangerous condition...

"Preparation of the colon for colonoscopy involves a cleansing of the large bowel by one of several different methods, in some of which large volumes of a liquid cleansing agent may be given: one method involves drinking 4 l polyethylene glycol solution; another involves taking 90 ml sodium phosphate solution.(5,9) Both methods can lead to diarrhoea with nausea, vomiting, and potential dehydration,(9) often resulting in raised plasma concentrations of antidiuretic hormone.(10) Thus electrolyte imbalance may occur, either from increased oral water intake with abnormal fluid retention or from increased fluid losses into the gastrointestinal tract.

Furthermore, preparation for colonoscopy causes substantial release of antidiuretic hormone,(10) and gastrointestinal fluid losses may cause excessive thirst, so increasing fluid intake. In patients with impaired ability to excrete water, the raised plasma antidiuretic hormone concentrations can lead to hyponatraemia; if thirst is impaired, excessive fluid losses can lead to hypernatraemia. In elderly patients in hospital, acute hypernatraemia and hyponatraemia may be fatal,(11,12) yet there are no reports of fatal electrolyte complications associated with elective colonoscopy. We recently saw three patients who developed symptoms of hypernatraemia or hyponatraemia (dysnatraemia) as a complication of elective colonoscopy." (British Medical Journal, BMJ, February 2003)

Renal Failure – This link explains renal failure related to polyethylene glycol.

http://www.ntuh.gov.tw/PMR/Lists/List14/Attachments/164/10253009-200903-37-1-45-50-a.pdf

Additional Kidney/Urinary/Blood symptoms

Failure to thrive
Urinary retention
Burning urination
Skin burns from urination
Elevated white blood cells
Recurring bacteria in urine (borderline urinary tract infections)
Cloudy urine
Elevated phosphates in urine
Elevated urinary calcium and phosphorus levels.
Hypocalcemia (low blood calcium), broken bones, bone pain, holes in teeth, discolored teeth, broken tail bone

B. Statement of Grounds, Continued

Adverse Events, Continued

Neuropsychiatric Symptoms

Parents have reported a myriad of neurological symptoms experienced by their children while on polyethylene glycol products, some residual and some permanent. A visit to the Miralax Yahoo Group http://health.groups.yahoo.com/group/miralax/ provides insight into the heart wrenching stories of parents in despair over the changes in their children while on these products. Children and families are suffering the extreme stress associated with the 'loss' of the children they once knew.

Anxiety
Phobias
Extreme nervousness
Obsessive-Compulsive behavior
Scratching, biting (self and others)
Nightmares
Hysteria
Memory loss
Sleeplessness
Irritability
Mood swings
Bipolar disorder
Withdrawal
Communication loss
Loss of concentration
Vertigo while lying down
Anger
Tantrums
Metabolic acidosis
Clawing sister's eyes
Sensitivity to sound
Motor skills affected
Fearfulness
Confusion
Inability to focus
Mumbled speech
Gait disturbance
Obsessive finger licking
Feelings of something dripping down face
Compulsive bad thoughts
'Meltdowns' over homework
'Meltdowns' over trivial things
'Panic' behavior
'Dr. Jeckyll & Mr. Hyde' behaviors
'Wave pool feeling' when trying to go to sleep
Tics
Tremors
Seizures
Violent behavior
Suicidal thoughts (age 6)
Aggression
Depression
Suspected encephalopathy
'Wild behavior'
Death threats (age 7)
Paranoia / bizarre hiding
Anti-social behavior
Slurred speech, whispering
Staring

* Death *

The attached FDA Adverse Event Reporting System reports include deaths in children while being administered polyethylene glycol products. Suicide and attempted suicide are also reported in the FDA Adverse Events Reporting System.

http://xa.yimg.com/kq/groups/12842967/1400876968/name/children.pdf

B. Statement of Grounds, Continued

Adverse Events, Continued

Other Events Reported with Polyethylene Glycol Use

Increased anion gap – excessive acids in the blood
Blood amylase increases - pancreas, liver function
Blood urea increased, urinary failure
Lipase increased - pancreas not working well
Urinary retention
Intestinal perforation
Cardiac failure
Petechiae - red dots on skin
Dysphonia - hoarseness in voice
Dyspnea - shortness of breath
Pharyngolaryngeal pain
Tongue odema - swelling
Brain odema - swelling
Neuropathy, retching
Chills
Eosinophil count - allergic reaction
Pruritus, itchy skin disorder
Nervous system disorder
Sudden death
Blood albumin decreased - not enough protein in blood
Renal tubular necrosis, renal failure
Blood Potassium decreased
Hypocalcemia
Blood sodium abnormal
Convulsions
Coma
Gait disturbance
Urticaria - hives
Shock
Erythema – skin reaction
Blood Pressure decreased
Hypercalcemia - high potassium
Blood electrolyte abnormal
Blood potassium decreased
Abdominal distention
Flushing
Peritonitis - lining of bowel inflamed
Enuresis - night wetting
Anaphylactoid reaction – immune response
Mouth ulceration
Tetnay, rigors – muscle contractions
Sudden death
Peeling of skin
Nausea
Gas
Extreme bloating
Abdominal pain

B. Statement of Grounds, Continued

Adverse Events, Continued

Encropresis, involuntary fecal soiling (due to loss of muscle control)
Ileus - paralysis of bowels
Bowel ecology imbalance, loss of probiotics
Rashes
Eczema

More Reports

Druglib.com reports 95 adverse events among Miralax users between April 2009 and March 2010.

http://www.druglib.com/adverse-reactions_side-effects/miralax/

Clinical Trials

Results Buried

Pharmaceutical industry funded clinical trials are on trial themselves. A study published in the Annals of Internal Medicine found that drug companies are not reporting results of all clinical trials and, in fact, are reporting positive outcomes in 85 percent of publications versus 50 percent for government funded studies.

"...The Annals study, led by Florence Bourgeois of Children's Hospital Boston and Kenneth Mandl of the Children's Hospital Informatics Program there, finds that of 546 drug trials conducted between 2000 and 2006 (the cutoff was to allow the trials several years to see the light of print), only 32 percent of those primarily funded by industry were published within 24 months of finishing. That compares with 56 percent of the trials funded by nonprofit or nonfederal organizations with no industry money. Combine that with another finding—that industry-funded trials reported positive outcomes in 85 percent of publications, compared with 50 percent for government-funded trials—and a worrisome specter emerges: industry is cherry-picking which of its clinical trials to publish, deep-sixing those that failed to show that a new drug is effective." (Newsweek August 5, 2010) http://www.thedailybeast.com/newsweek/2010/08/05/some-pharmaceutical-clinical-trial-results-are-buried-study-shows.html

Parents wonder if there are unpublished PEG 3350 clinical trials showing negative results.

Lacking Long Term Follow-up

Children are being used in clinical trials of this potentially dangerous product, while thousands of adverse events have been reported and not investigated. Miralax is not FDA approved as a bowel preparation before colonoscopy.

In the clinical trial, The Efficacy, Side Effects, and Tolerance of Polyethylene Glycol 3350 as A Bowel Prep in Children conducted by Cleveland Clinic, http://clinicaltrials.gov/ct2/show/NCT01164410 it was concluded that "Miralax TM combined with Gatorade GTM given the day prior to colonoscopy is a safe, tolerable and efficacious cleansing regimen for bowel prep in children." The study results are not posted and the study does not outline any follow-up protocol to determine whether the children studied suffered any lasting adverse effects from the large dose of polyethylene glycol ingested.

B. Statement of Grounds, Continued

Children Are Not Small Adults

Developing Systems, Drug Interactions, GI and Kidney Conditions, Allergies

As medical science has known for a decades, safe dosing for children cannot be established by simply reducing an adult dose of a drug. Further, some doctors are not reducing the dose for children and are actually increasing dosing to many times the adult dose. Adjusting dosing for reduced body weight, when it does happen, does not take into account the many differences in the developing immune system and organs of children, especially the brain, which scientist now know does not cease developing until well into the 20's.

Often children with constipation have food intolerances, which may be the root cause of their bowel issues. Leaky Gut Syndrome and other bowel disorders may go unrecognized with the rush to treat with polyethylene glycol products. Some parents whose children have not experienced permanent damage with PEG use have reported improvement when PEG was discontinued and nutritional protocols employed.

PEG is a laxative that increases the amount of water in the intestinal tract to stimulate bowel movements. Children with allergies may be on allergy medicines which also have a diuretic effect. One mother, a registered nurse, reported an impulsive and inexplicable criminally violent act performed by her son while on a combination of PEG and an allergy medicine. She suspects metabolic encephalopathy, a known side effect of polyethylene glycol use http://ndt.oxfordjournals.org/content/18/12/2486.full. This article explains the relationship between hyponatremia and encephalopathy.
http://www.springerlink.com/content/g1658566127v4g68/

Drugs.com reports 165 drugs known to have a moderate interaction with polyethylene glycol 3350, (594 brand and generic products). http://www.drugs.com/drug-interactions/polyethylene-glycol-3350-index.html?filter=2 Moderate interactions are described as "Moderately clinically significant. Usually avoid combinations; use it only under special circumstances."

Miralax packaging tells consumers not to use the product if they have kidney disease or are allergic to PEG. Parents may not know whether children have kidney disease, as it can go undetected until an event makes it necessary to test for it. PEG is being prescribed without urinalysis or blood work. Children are not being tested for PEG allergy.

B. Statement of Grounds, Continued

Toxics

As stated in the Public Summary of the FDA Drug Safety Oversight Board Meeting on PEG products, "children may be more susceptible to variations in PEG product quality."

Ethylene Glycol / Diethylene Glycol

Also according to the Public Summary of the FDA Drug Safety Oversight Board Meeting on PEG products, "Approved products instruct patients to dissolve the PEG-3350 powder in a liquid and use immediately. The approved products have been tested under these conditions and are stable. **It is unknown if prolonged duration in solution would change the chemical properties of PEG-3350, and what the actual content of ethylene glycol or diethylene glycol** or other low molecular weight PEG would be under such conditions."

Parents wonder, does this statement mean that PEG 3350 may break down into ethylene glycol or diethylene glycol in the body?

Ethylene Glycol is the major ingredient in antifreeze and extremely toxic to humans.

Diethylene Glycol is another poisonous ingredient in antifreeze. In 1937 many children died from diethylene glycol toxicity when diethylene glycol was added to sulfanilamide to improve solubility.

Again, up to 90% of NICU patients are exposed to drugs that are either unlabeled or used in an off-label manner. In 1937, sulfanilamide was compounded with diethylene glycol to improve solubility; 107 patients, many of them children, died due to diethylene glycol toxicity. In 1981, the neonatal gasping syndrome secondary to benzyl alcohol toxicity was reported. Extremely low birth weight (ELBW) infants receive significant numbers of medications, putting them at risk for acute and chronic exposure to single or multiple excipients.

Diethylene glycol is involved in mass poisonings around the world.
http://www.absoluteastronomy.com/topics/Diethylene_glycol

Diethylene glycol causes kidney and liver damage.

http://www.nicnas.gov.au/Publications/CAR/Other/DEG_Hazard_Assessment_Report_PDF.pdf

1,4 –Dioxane

Since the 1970's, FDA has tested the presence of 1,4-dioxane, a probable carcinogen linked to breast cancer in PEG used for cosmetics. Is PEG 3350 a source of 1,4 dioxane and should it be tested?

http://healthychild.org/issues/chemical-pop/dioxane/

Aluminum

This article states that untreated PEG in weights over 3000 can be contaminated with heavy metals, including Aluminum, a neurotoxin. What testing is done to ensure that no heavy metals are in PEG 3350 final products?

http://www.plantphysiol.org/content/61/4/708.full.pdf

B. Statement of Grounds, Continued

Use of Miralax in Bowel Preparations

In addition to the reports of parents on the Miralax Yahoo Group, we have learned that doctors routinely prescribe Miralax as a bowel preparation before colonoscopy – another off-label use. The following article on the dangers of Miralax as a bowel preparation appeared in a 2009 issue of Gastroenterology & Hematology.

Use of MiraLAX in Bowel Preparations

MiraLAX (polyethylene glycol [PEG] 3350) is a laxative approved for the treatment of mild or occasional constipation. Several reports have indicated that clinicians often include MiraLAX as an alternative bowel preparation in the purgative armamentarium, however. Although MiraLAX has been used safely in a large body of patients, serious safety concerns have been raised regarding its off-label use as a bowel preparation. First, MiraLAX is not indicated by the US FDA for use as a bowel preparation before colonoscopy. Furthermore, no controlled clinical trials have been performed to assess the relative safety and efficacy of MiraLAX for colon cleansing. When used as a laxative, MiraLAX is not recommended for patients with kidney disease due to concerns of excessive depletion of the extracellular fluid volume (dehydration or, more accurately, volume depletion). These patients are at an even greater risk of volume depletion and potential electrolyte disturbances when MiraLAX is taken as a bowel preparation at a dose of 14 times (238 g) higher than the recommended laxative dose. Unlike PEG-based purgatives indicated for bowel preparation, MiraLAX does not contain a built-in electrolyte replacement solution (ELS), compounding the risk of fluid-electrolyte imbalance. Diarrhea induced by PEG-based laxatives correlates with volume depletion and electrolyte imbalance. In an attempt to limit this problem, MiraLAX is often administered in combination with a hydrating sports drink (eg, Gatorade®; PepsiCo, Inc, Purchase, NY) to boost electrolytes. While sports drinks can aid in the rehydration of athletes during physical exertion, the electrolyte load is insufficient for patients undergoing a purgative regimen. Notably, PEG-ELS bowel preparations contain roughly 9 times more sodium (grams per regimen) than a sports drink (Table (Table3).3). Sports drinks replace carbohydrates and electrolytes by rapidly moving sugar, electrolytes, and free water into the circulation, thereby increasing overall plasma volume.25 Metabolism of the carbohydrate component leads to a net absorption of "free" water (water without associated electrolytes). This absorption of free water may pose an increased risk of water imbalance for patients with impaired water handling and may contribute to the development of hyponatremia.26

Use of Miralax in Bowel Preparations, Continued

Risk of Hyponatremia

The administration of purgatives can lead to hyponatremia by a variety of overlapping mechanisms. Hyponatremia, or the relative increase in the ratio of body water to sodium, usually occurs in the setting of increased levels of circulating antidiuretic hormone (ADH).27 Antidiuretic hormone and water intake play primary roles in defending body water content; as circulating osmolality increases above a threshold of ~285 mOsm/kg, thirst is stimulated and the posterior pituitary is stimulated to release ADH. Volume depletion decreases this osmotic threshold for ADH release and augments ADH release as a function of systemic osmolality.28 The volume depletion associated with purgative administration will thus lead to an increase in circulating ADH.29 Nausea, frequently associated with purgative administration, is a very potent stimulus for ADH release.27 Baseline ADH levels and/or the ADH response to volume depletion are also increased in patients taking certain medications, particularly thiazide diuretics and selective serotonin reuptake inhibitors, and in patients with hypervolemic disorders associated with increases in circulating ADH, such as congestive heart failure or cirrhosis. Other drugs, particularly nonsteroidal antiinflammatory drugs (NSAIDs), potentiate the renal response to ADH. In summary, the administration of purgatives, comorbid processes such as congestive heart failure, and patient medications all increase circulating ADH levels in patients receiving purgatives, which in turn leads to the retention of ingested free water and hyponatremia.

The sudden decrease in serum osmolality that occurs with purgative-associated hyponatremia and other causes of hyponatremia leads to an influx of water into cells down the new osmotic gradient. This influx of water can cause rapid brain swelling (cerebral edema) if the physiological response mechanisms are overwhelmed, leading to the various symptoms and signs of hyponatremic encephalopathy. Early stages of hyponatremic encephalopathy include nausea, vomiting, and mental confusion; more serious sequelae include neurogenic pulmonary edema, hypoxia, seizure, and death.30 For reasons that are not entirely clear, severe hyponatremic encephalopathy is almost entirely limited to female patients, particularly those who are premenopausal.

Acute hyponatremic encephalopathy has been associated with several methods of bowel preparation, including PEG-ELS, oral NaP, and off-label use of MiraLAX plus Gatorade.26,27,31 To investigate the frequency of hyponatremia in patients undergoing colonoscopy, Cohen et al29 followed 40 patients from initial bowel preparation with PEG-ELS to 1 hour after colonoscopy, measuring serum sodium and ADH levels. Initially, serum sodium and ADH levels were normal; however, after bowel cleansing and immediately before colonoscopy, 25% of patients had elevated serum ADH levels. Eight percent of patients experienced a decrease in serum sodium concentration to <130 mmol/L after colonoscopy.29 The relative frequency of purgative-associated hyponatremia associated with PEG-ELS versus OSPS versus MiraLAX plus Gatorade is not known, nor is the relative risk known for severe hyponatremic encephalopathy. However, the relative risk of purgative-associated volume depletion is expected to be greater for MiraLAX plus Gatorade, given that this preparation does not provide enough electrolytes to replenish PEG-associated intestinal losses. The carbohydrate content of Gatorade is expected to lead to a greater gain of free water, with an augmentation of intestinal water absorption followed by metabolism of the absorbed carbohydrate.25 MiraLAX plus Gatorade is thus hypothesized to increase the risk of purgative-associated hypovolemia, and thus the risk of hypovolemic increases in ADH, and promote the absorption of excess free water; these 2 factors are hypothesized to predispose colonoscopy patients to acute hyponatremia. However, at the current time, these statements have not been validated through clinical studies, and further investigation is warranted.

B. Statement of Grounds, Continued

Parents Need Answers

Bacteria

As mentioned earlier, in the study Fatal Dysnatremia Caused by Elective Colonoscopy, three patients died after being administered a PEG colon cleanse.

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021551s000_HalfLytely%20Tabs_medr.PDF

On the website of the Bristish Medical Journal, one physician responding to the article replied, "I find it difficult to believe that intestinal secretion was the cause of the complications or deaths unless these patients had the unappreciated presence of gut mucosal ischaemia or bacterial infection such as C difficle." This leads parents to wonder what bacteria present in the gut may interact with polyethylene glycol in a way that may cause dangerous complications.

One member of the Miralax Yahoo Group is a molecular biologist who questions whether PEG may break down in the presence of bacteria. As a number of different bacteria populate the gut, could polyethylene glycol break down into ethylene glycol in the body?

This article describes the breakdown of PEG exposed to bacteria in sewage. Although a completely different environment, parents wonder what specific to bacteria may cause the breakdown.

http://www.sciencedirect.com/science/article/pii/0043135477901890

Polyethylene Glycol Blocks Protein Absorption

Polyethylene Glycol is known to block the absorption of protein.
http://www.waset.org/journals/waset/v49/v49-30.pdf
If this is the case, what effect does PEG have on the absorption of protein in children who are on long term polyethylene glycol treatment? One mother on the Miralax Yahoo Group reports a cessation of weight gain in her daughter from the time she began taking polyethylene glycol until she stopped. Could this be due to protein being blocked by PEG? What are the effects on children's brains of this important nutrient possibly being blocked by PEG?

Aspiration

One child who died while being administered PEG 3350 aspirated because the products was administered through an NG (nasalgastric) tube. One group member wonders if a child could aspirate polyethylene glycol if administered at home through a bottle or sippy cup while lying down, or if PEG is vomited after ingestion.

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021551s000_HalfLytely%20Tabs_medr.PDF

Polyethylene Glycol Absorbs Heat

Fabrics are now being treated with polyethylene glycols to absorb heat in high temperatures and release it when temperatures cool. http://www.ars.usda.gov/is/AR/archive/may96/cotton0596.pdf

What effect does PEG's heat absorption property have on human health and on the brains and nervous systems of children in particular?

B. Statement of Grounds, Continued

Parents Need Answers, Continued

Polyethylene Glycol and Teeth and Bones

Parents report holes in teeth, discoloration of teeth, and broken bones while their children are using polyethylene glycol. Regarding PEG 3350 and children's health, this site recommends, "Take care of your child's teeth. See a dentist often." http://kidshealth.org/teen/medications/polyethylene_glycol_3350.html

Ethylene glycol toxicity results in hypocalcemia due to calcium being consumed in circulation http://emedicine.medscape.com/article/814701-overview#a0104. Hypocalcemia is also reported in polyethylene glycol adverse events.

What is the connection between polyethylene glycol and dental and bone health?

Alternative to Colonoscopy Preparations

Colon Hydrotherapy

While some doctors will prescribe magnesium citrate products for bowel cleanse, most will prescribe PEG products. Danbury Hospital in Danbury Connecticut is the first hospital in the country to offer colon hydrotherapy as a colon cleanse before colonoscopy.

http://www.i-act.org/Resources/Danbury%20Hospital.pdf

Dr. Chris Demitriou, a gastroenterologist with a practice on Long Island, NY, performs an average of 1600 colonoscopies per year using colon hydrotherapy preparation with good results.

http://www.endonurse.com/articles/2011/12/bowel-preps-2012-is-hydrotherapy-part-of-the-mix.aspx

What is being done to make this option available nationwide for people who choose not to ingest PEG or give it to their children?

PEG Test Kits

The company below makes PEG test kits for use in animals. When will testing be available for testing PEG levels in humans?
http://www.lifediagnostics.com/peg-reagents.php

B. Statement of Grounds, Continued

Conclusion

The effectiveness of a polyethylene glycol laxative is measured by the number of stools produced or the 'cleanliness' of the bowel after use. All the while, the work of the chemical and its component chemicals circulating through the body over a prolonged duration, including its effects on the brain and nervous system have not been tested. Parents offer a convincing body of knowledge about their children's health and wellbeing, and while not evidence discovered in a laboratory setting, this body of knowledge can be crucial to uncovering safety issues present in a consumer health product. The FDA designed the Adverse Event Reporting System for precisely this reason.

Given all the known properties of polyethylene glycol - water absorption, heat absorption, protein blocking, abrasive effect, etc., why are studies not performed to test the effects of these properties on the whole body? Why are the polyethylene glycol related symptoms reported by parents so similar to those of ethylene glycol toxicity and why is a drug with so many reported adverse events being marketed against manufacturer labeling to children? Parents are stumped - and angry.

We hope that by submitting this petition, the FDA will open a thorough investigation of polyethylene glycol use this year. As word of polyethylene glycol adverse events spreads, parents are becoming more aware and are looking to the federal government to issue warnings on the dangerous effects experienced by polyethylene glycol users and outlined by the FDA Drug Safety Oversight Board in 2009. The parents who started the Miralax Yahoo Group have been searching for answers for 10 years. If these effects can be proved to result from polyethylene glycol use, both they and Empire State Consumer Project would like to spare additional children and families the suffering they have endured.

C. Environmental Impact

Not applicable at this time.

D. Economic Impact

Not applicable at this time.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Regarding additional comments, in accordance with Section (d), 'An interested person may submit written comments to the Division of Dockets Management on a filed petition, which comments become part of the docket file. The comments are to specify the docket number of the petition and may support or oppose the petition in whole or in part. A request for alternative or different administrative action must be submitted as a separate petition.'

Sincerely,

Carol Chittenden

Carol Chittenden
Empire State Consumer Project
50 Landsdowne Lane
Rochester, New York 14618
cachitter@aol.com 585-831-7124

F. Attachments

1. Parent Statements – 1-54

2. Adverse Events

   7 adverse events November 2000

   54 adverse events April 2001

   89 adverse events March 2002

   161 adverse events October 2003

   238 adverse events September 2004

   447 adverse events January 2006

   665 adverse events April 2007

   869 adverse events March 2008

   1,014 adverse events October 2009

   1,966 adverse events June 2011

   2,257 adverse events March 2012

3. Jeanie Ward's original petition from 2001

4. FDA Correspondence letter dated November 14, 2001

5. FDA Correspondence letter dated February 20, 2002

6. Key to adverse events

7. Miralax Yahoo Group home page

8. Summary of pertinent adverse events

9. Golytely Solution for Colonoscopy Preparation article

10. Miralax Insert, Do Not Give to Children

11. Food and Drug Oversight Board Meeting, June 18, 2009

12. Fatal Disnatraemia Article Rapid Response Carlos Ayus

13. FOIA adverse events of children and adults / individual reports - page 13-1 through page 13-26

    Deaths, Suicide, Rage / Anxiety

F. Attachments, Continued

13. FOIA adverse events of Children and Adults / Individual Reports, Continued

    Seizures

    Aspiration

    Hyponatremia

    Kidney Failure

    Failure to Thrive

    Tics

    Acute Tubular Necrosis

    Stopped Breathing

    Burning Sensation

14. Allied Lab Test for Composition of Miralax

15. Urinary Excretion of Polyethylene Glycol 3350 article

16. March 2002 Formulary Editions, Miralax Not Completely Recovered in Constipated Patients

17. Neurologist's statement on Miralax

18. Nexgen manufacturer's letter Not to give to pediatrics

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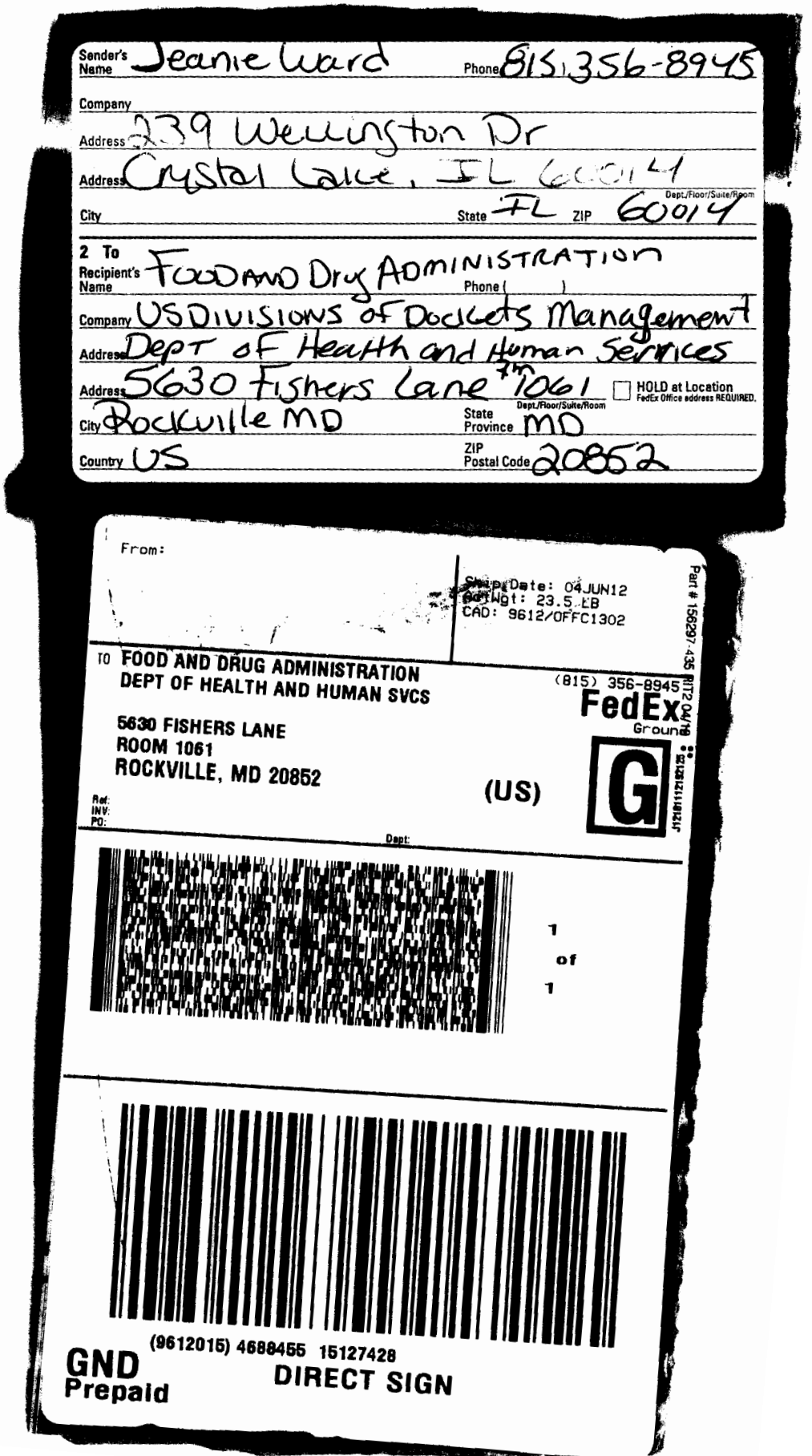

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