FACT SHEET

ESCP

Empire State Consumer Project, Inc.

Protecting children, consumers, and the environment since 1971.

Polyethylene Glycol 3350 Laxatives and Children

Empire State Consumer Project, Inc. (ESCP) is a registered 501c3 Not-for-Profit Organization dedicated to reducing the use of unsafe products and chemicals toxic to human and environmental health. We accomplish this by educating consumers and industry, conducting product testing and reporting, and by advocating for regulation where needed to protect the public interest. www.empirestateconsumerproject.blogspot.com

Introduction

Due to serious safety concerns raised in an FDA Citizen Petition filed by Empire State Consumer Project (ESCP), in 2013, the US Food and Drug Administration (FDA) agreed to study the effects of polyethylene glycol 3350 (PEG 3350) laxative use in children and issued a grant to the Children's Hospital of Philadelphia to conduct the study. ESCP submitted the petition in 2012 on behalf of parents who say their children have been harmed by polyethylene glycol 3350 drug products.

There is special concern about the safety of PEG 3350 laxatives like Miralax, which are not approved for use in children, and are not approved for more than seven days use. Many children are prescribed multiple daily adult doses by doctors off-label, often for months or years at a time.

The ESCP petition calls for an investigation into the effects of PEG 3350 on children and a boxed warning on PEG 3350 products. The boxed warning was not granted, but the FDA has decided to update the labeling of prescription PEG 3350 bowel preparations with more stringent warnings and precautions for patients with certain health conditions.

Toxicity

The safety concerns reported in the FDA Citizen Petition are symptoms similar to those of ethylene glycol toxicity. The petition grant includes an agreement by FDA to study the potential for PEG 3350 to degrade into ethylene glycol (EG) and diethylene glycol (DEG), and to study the long term effects of PEG 3350 products on pediatric patients. Ethylene glycol and diethylene glycol are chemicals used to make antifreeze. Both are toxic to the central nervous system, liver, and kidneys when ingested. In recent history, DEG contaminated cough and acetaminophen syrups killed hundreds of adults and children. In 2007, the FDA issued a warning for consumers not to buy toothpaste from China, as some brands were made with DEG.

In addition to the ethylene glycol and diethylene glycol children may be exposed to through the degradation of PEG 3350, the FDA has tested 8 lots of polyethylene glycol 3350 and found ethylene glycol and diethylene glycol contaminants in the product itself… “To better understand the level of polyethylene glycol impurities in PEG, the FDA Chemistry and Manufacturing group evaluated PEG 3350. This analysis of eight lots of PEG 3350 confirmed the presence of small amounts of ethylene glycol and diethylene glycol in all lots tested. Based upon the recommended daily adult dose of 17 mg daily dose PEG 3350, the maximum daily exposure of ethylene glycol would be 0.005 mg/kg/day for a 60 kg patient, or 0.015 mg/kg/day for a 20 kg pediatric patient (approx 5 years of age). Other low molecular weight (LMW) PEGs were not included in this analysis. However, it is not known if any of these LMW species are absorbed and if so to what extent. Understanding the human absorption profile of LMW species is the first step needed in trying to understand the possible contribution of PEG 3350 use to the development of adverse events in children using this product chronically.” Although another FDA test did not show the presence of EG and DEG, we have asked the FDA to perform ongoing testing of PEG 3350 products to show whether EG and DEG are contaminants.

Empire State Consumer Project has since petitioned the FDA to issue a Drug Safety Communication regarding the finding of ethylene glycol and diethylene glycol in all lots of PEG 3350 it tested, so that parents of study participants and all parents can be made aware of the potential for PEG 3350 to contain ethylene glycol and diethylene glycol. This petition for a Drug Safety Communication was denied.

The EPA recommends that children not be exposed to more than 20 mg/L or 20 parts per million (ppm) of ethylene glycol in drinking water per one day or 6 mg/L or 6 ppm per day over 10 days. The adult doses of PEG 3350 tested were found to contain 0.3 mg of ethylene glycol of daily exposure for a 44 lb. child. This exposure is in addition to any EG and DEG exposure that may be found to occur from PEG 3350 degradation of the laxative products. The health effects of long term exposure of children to PEG 3350 are not known, although risks from short term exposure to EG and DEG are well documented in humans.

Although PEG 3350 laxatives have been studied for their effectiveness in producing a bowel movement, NO study has ever been done on neuropsychiatric effects in children and NO study has ever been done on the long term use of these products in children.

Adverse Events

The FDA Adverse Event Reporting System (FAERS) shows over 19,000 adult and child adverse event reports that include at least one PEG 3350 product, including a number of deaths. The number of reports rose from 2,257 in 2012, when the FDA Citizen petition was filed. In 2009, the FDA Drug Safety Oversight Board acknowledged neuropsychiatric, metabolic, gastrointestinal, and kidney events in children who took PEG 3350 laxatives, but felt that "no action was required" at that time:

"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." "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."

Doctors at the National Taiwan University Hospital in Taipei have concluded "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." http://www.ntuh.gov.tw/pmr/lists/list14/attachments/164/10253009-200903-37-1-45-50-a.pdf

Dosing

As stated in our petition, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NSAPGHAN) has created guidelines for off-label prescribing of PEG 3350 laxatives to children. These guidelines are not approved by the FDA. Parents report that many doctors are prescribing even higher doses. Children are often given multiple adult doses daily for months and years at a time.

Based on NASPGHAN dosing, one gram of PEG 3350 per kg of body weight is 10 grams of PEG for a 22 lb. child, or more than half of the 17 gram adult dose.
http://journals.lww.com/jpgn/fulltext/2006/09000/evaluation_and_treatment_of_constipation_in.28.aspx

In an example of a constipation treatment recommendation from a large children's hospital in the US, dosing is 3 times per day for 3 days during the cleanout phase and a duration of 6-12 months or more for the maintenance phase. In this case, a 10 year old child would receive 3 adult daily doses per day for 3 days, then 1-2 adult daily doses per day for up to a year or more. Again, much younger children are also routinely given adult doses of PEG 3350 daily for months and years at a time… "As soon as they complete the first cleanout, give polyethylene glycol once daily at the following dosages. Mix in juice or water, not milk. It needs to be taken daily for at least 6-12 months and often longer. You can increase the dose slightly if needed.

- Children 18 months to 5 years old – Give 2 teaspoons, mixed in 4 to 6 ounces of fluid
- Children 5 to 10 years old – Give 1 capful (17 gms) mixed in 6-8 ounces of fluid
- 10 years old and older – Give 1 to 2 capfuls mixed in 8 ounces of fluid"

2017 Update:

At our request, in 2016, doctors at the Research Institute at National Children's Hospital in Columbus, Ohio agreed to conduct a study of the effects of PEG 3350 on the behavior and gut biology of mice.

This FDA document, updated in 2016 shows that the FDA acknowledged years ago that Miralax causes seizures (45th page): http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203595Orig1s000OtherR.pdf

Adverse event reports that include at least one PEG 3350 product are now over 19,000. We have contacted the FDA regarding the progress of the study at Children's Hospital of Philadelphia (CHOP) to express our concern that the study be a comprehensive assessment of the effects of PEG 3350 use in children. Rather than making the assumption that absorption alone is leading to neuropsychiatric symptoms in children, we have asked the FDA to include the following testing in CHOP's research. We feel that if PEG testing alone does not prove that EG or DEG is being absorbed, we have lost the opportunity to look for other factors that may be contributing to neuropsychiatric symptoms in children. We are still awaiting answers from the FDA on the start of the study and an earlier Freedom of Information request.

As we asked in our FDA petition, what are the effects of chronic laxative use on nutrient absorption and depletion in children? Many nutrients, including B vitamins and magnesium are related to neuropsychiatric health. If there is evidence that chronic laxative use blocks nutrient absorption or depletes nutrients, what key nutrients can be measured while blood is being drawn for PEG, EG, DEG?

Effects of chronic laxative use on the enteric nervous system and feedback to the central nervous system. As we asked in our petition, what effects does peg laxative use have on intestinal flora? How does this affect the nervous system in the intestines that would impact neuropsychiatric health? If it is true that 95% of seratonin is found in the bowels and that 90% of the fibers in the vagus nerve transmit information from the gut to the brain and not the other way around (http://www.scientificamerican.com/article/gut-second-brain/), can we measure this effect in children on PEG 3350 through blood and stool testing?

Metabolic acidosis was acknowledged by the 2009 FDA Drug Safety Oversight Board as an adverse event related to PEG 3350 use in children. As metabolic acidosis is a cause of demylenation of nerves (as is B12 deficiency) and related neuropsychiatric symptoms, will metabolic acidosis be tested for in children being studied?
http://www.merckmanuals.com/home/brain_spinal_cord_and_nerve_disorders/multiple_sclerosis_ms_and_related_disorders/overview_of_demyelinating_disorders.html

http://www.nationalmssociety.org/For-Professionals/Clinical-Care/Diagnosing-MS/Signs-and-Symptoms-Consistent-with-Demyelinating-D#section-6

Resources

Empire State Consumer Project FDA Citizen Petition and FDA Response
http://www.regulations.gov/#!searchResults;rpp=25;po=0;s=FDA-2012-P-0566;fp=true;ns=true

NIH Grant to Study PEG 3350 and Test of 8 Lots
http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-14-088.html

Empire State Consumer Project and Reply to FDA Petition Response
http://www.empirestateconsumerproject.blogspot.com

New York Times Article on Petition, Science Times
http://www.nytimes.com/2015/01/06/science/scrutiny-for-a-childhood-remedy.html?_r=0

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