

Drug Class Review Monograph – GPI Class 47 – Antidiarrheals

Review Time Frame: 02/2016 – 01/2017

Previous Class Review: 11/2016

Background:

Antidiarrheal agents are used for the symptomatic treatment of diarrhea. Gastrointestinal agents that are commonly used to help stop diarrhea include:

- Anti-peristaltic agents- inhibit gastrointestinal (GI) motility and slow excess GI propulsion; interfere with peristalsis by a direct action on the circular and longitudinal muscles of the intestinal wall to slow motility
- Bismuth subsalicylate- exhibits both anti-secretory and antimicrobial action against bacterial and viral gastrointestinal pathogens
- Chloride channel antagonists (e.g., Fulyzaq)- inhibit cyclic adenosine monophosphate (cAMP)-stimulated cystic fibrosis transmembrane conductance regulator (CFTR) chloride ion channel and calcium activated chloride ion channels at the enterocyte luminal membrane which regulates fluid secretion and water loss (high volume) due to diarrhea, normalizing chloride ion and water flow in the GI tract
- Probiotics- help to re-establish normal intestinal flora

New treatment guideline recommendations:

- The American College of Gastroenterology (ACG) recommends the following for the management of acute diarrheal gastrointestinal infections in adults:
 - In patients receiving antibiotics for traveler’s diarrhea, adjunctive loperamide therapy should be administered to decrease duration of diarrhea and increase chance for a cure. (Strong recommendation, moderate level of evidence)
 - Bismuth subsalicylates can be administered to control rates of passage of stool and may help travelers function better during bouts of mild-to-moderate illness. (Strong recommendation, high level of evidence)
 - The use of probiotics or prebiotics for the treatment of acute diarrhea in adults is not recommended, except in cases of post antibiotic-associated illness. (Strong recommendation, moderate level of evidence)

Newly approved drugs:

- None identified

Newly approved formulations:

- None identified

Newly approved generics:

- None identified

Discontinued drugs:

- None identified

FDA Safety Alerts/black box warnings:

- 06/07/2016: FDA Drug Safety Communication: FDA warns about serious heart problems with high doses of the antidiarrheal medicine loperamide (Imodium), including from abuse and misuse (refer to page 3 for full detail).

Pipeline alerts:

Agents pending FDA approval include:

- None identified

References:

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2017. Available at: <http://www.clinicalpharmacology-ip.com/>.
2. Bismuth subsalicylate. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Hudson, OH. Available at: <http://online.lexi.com>. Accessed January 13, 2016.
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4. US Script Oracle PBM: Medi-Span® Master Drug Data Base. February 2017.
5. Food and Drug Administration. Available at: www.fda.gov.
6. Riddle MS, DuPont HL, Connor BA. ACG clinical guideline: diagnosis, treatment, and prevention of acute diarrheal infections in adults. *Am J Gastroenterol* 2016; 111:602–622.

(FDA Drug Safety Communication, continued from page 2)

FDA Drug Safety Communication: FDA warns about serious heart problems with high doses of the antidiarrheal medicine loperamide (Imodium), including from abuse and misuse *(11/2016 update: The issues described below have been addressed in product labeling. Health care professionals and patients can access the approval letter and latest prescribing information for Imodium.)*

[06/07/2016]

The U.S. Food and Drug Administration (FDA) is warning that taking higher than recommended doses of the common over-the-counter (OTC) and prescription diarrhea medicine loperamide (Imodium), including through abuse or misuse of the product, can cause serious heart problems that can lead to death. The risk of these serious heart problems, including abnormal heart rhythms, may also be increased when high doses of loperamide are taken with several kinds of medicines that interact with loperamide (e.g., cimetidine, clarithromycin, erythromycin, gemfibrozil, itraconazole, ketoconazole, quinidine, quinine, ranitidine, ritonavir).

The majority of reported serious heart problems occurred in individuals who were intentionally misusing and abusing high doses of loperamide in attempts to self-treat opioid withdrawal symptoms or to achieve a feeling of euphoria.

Health care professionals should be aware that use of higher than recommended doses of loperamide can result in serious cardiac adverse events. Consider loperamide as a possible cause of unexplained cardiac events including QT interval prolongation, Torsades de Pointes or other ventricular arrhythmias, syncope, and cardiac arrest. In cases of abuse, individuals often use other drugs together with loperamide in attempts to increase its absorption and penetration across the blood-brain barrier, inhibit loperamide metabolism, and enhance its euphoric effects. If loperamide toxicity is suspected, promptly discontinue the drug and start necessary therapy. If loperamide ingestion is suspected, measure blood levels, which may require specific testing. For some cases of Torsades de Pointes in which drug treatment is ineffective, electrical pacing or cardioversion may be required.

Advise patients taking loperamide to follow the dosing recommendations on the label because taking higher than recommended doses, either intentionally or unintentionally, may lead to abnormal heart rhythms and serious cardiac events leading to death. Also advise patients that drug interactions with commonly used medicines also increase the risk of serious cardiac adverse events. Refer patients with opioid use disorders for treatment.

Patients and consumers should only take loperamide in the dose directed by their health care professionals or according to the OTC Drug Facts label. Do not use more than the dose prescribed or listed on the label, as doing so can cause severe heart rhythm problems or death. If your diarrhea lasts more than 2 days, stop taking loperamide and contact your health care professional. Seek medical attention immediately by calling 911 if you or someone taking loperamide experiences any of the following:

- Fainting
- Rapid heartbeat or irregular heart rhythm

- Unresponsiveness, meaning that you can't wake the person up or the person doesn't answer or react normally

Ask a pharmacist or your health care professional if you are not sure how much loperamide to take, how often to take it, or whether a medicine you are taking may interact with loperamide. Always tell your health care professionals about all the medicines you are taking, including OTC medicines.

Loperamide is approved to help control symptoms of diarrhea, including Travelers' Diarrhea. The maximum approved daily dose for adults is 8 mg per day for OTC use and 16 mg per day for prescription use. It is sold under the OTC brand name Imodium A-D, as store brands, and as generics.

In the 39 years from when loperamide was first approved in 1976 through 2015, FDA received reports of 48 cases of serious heart problems associated with use of loperamide. This number includes only reports submitted to FDA, so there are likely additional cases about which we are unaware. Thirty-one of these cases resulted in hospitalizations, and 10 patients died. More than half of the 48 cases were reported after 2010. The serious heart problems occurred mostly in patients who were taking doses that were much higher than recommended. In other cases, patients were taking the recommended dose of loperamide, but they were also taking interacting medicines, causing an increase in loperamide levels. Additional cases of serious heart problems associated with the use of loperamide were reported in the medical literature. Cases reported to FDA and in the medical literature indicate that individuals are taking significantly high doses of loperamide in situations of both misuse and abuse, often attempting to achieve euphoria or self-treat opioid withdrawal. They are also combining loperamide with interacting drugs in attempts to increase these effects.