Comments to CMS regarding selected drugs for price negotiation (round 2)

Pursuant to the Inflation Reduction Act (IRA) of 2022 (P.L. 117-169) and in direct response to a call for information from the Centers for Medicare & Medicaid Services (CMS), Public Citizen offered the following five comments regarding drugs that are the subject of price negotiations in the context of the Medicare program. These comments aim to give CMS information that it can use to negotiation fair prices for these and related drugs moving forward. The comments, reproduced verbatim below, were posted at the dedicated CMS submission portal on March 1, 2025.

Comment listing:

1. fluticasone-umeclidinium-vilanterol (**Trelegy Ellipta**); for asthma, COPD
2. linaclotide (**Linzess**); for chronic idiopathic constipation or irritable bowel syndrome with constipation
3. linagliptin (**Tradjenta**); for type 2 diabetes
4. metformin-sitagliptin (**Janumet**); for type 2 diabetes
5. rifaximin (**Xifaxan**); for hepatic encephalopathy or irritable bowel syndrome with diarrhea

---

0a. Drug →→ Fluticasone furoate, umeclidinium, and vilanterol (**Trelegy Ellipta**)

0b. Author →→ Nina Zeldes, M.Sc., Ph.D.

Question 50a: On which indication(s) (which includes off-label use(s) per the definition provided in the instructions) of the selected drug would you like to provide input? (0/6000 characters, *including spaces*)

Enter text here (Q50a) →→ maintenance treatment of patients with chronic obstructive pulmonary disease (COPD) and maintenance treatment of asthma in patients aged 18 years and older.

I52: (Comparative Clinical Evidence)

Question 52c: For the indication(s) of the selected drug, identify any relevant evidence evaluating the clinical comparative effectiveness (e.g., clinical efficacy, real-world effectiveness, or safety) of the selected drug and potential therapeutic alternatives. Relevant comparative evidence may include but is not limited to: head-to-head randomized controlled trials, pragmatic clinical trials, network meta-analyses, observational studies, and real-world evidence. Provide supporting citations. (0/36,000 characters)

Enter text here (Q52c) →→ Fluticasone furoate, umeclidinium, and vilanterol (Trelegy Ellipta) is a fixed-dose, dry powder inhaler containing three drug classes: fluticasone furoate, an inhaled corticosteroid (ICS), umeclidinium, a long-acting anti-muscarinic (LAMA), and vilanterol, a long-acting beta agonist (LABA).[ref 1]

According to the prescribing information, Trelegy Ellipta is indicated for a relatively broad patient population: as maintenance treatment of patients with chronic obstructive pulmonary disease (COPD) and as maintenance treatment of asthma in patients aged 18 years and older. [ref 2] Importantly however, triple therapy such as with Trelegy Ellipta is only recommended as maintenance treatment for COPD patients for whom exacerbations are no longer adequately controlled with dual therapy, [refs 3-4] and in individuals whose asthma remains uncontrolled on dual therapy. [ref 5]

This is particularly noteworthy, as all three components of Trelegy Ellipta are associated with serious adverse events including the following: [ref 6]

- Treatment with corticosteroids, such as an ICS, increases several risks, including the risk of *Candida albicans* infections in the mouth and phalanx, the risk for lower respiratory tract infections (such as pneumonia), the risk of glaucoma and cataracts, as well as decreased bone mineral density.
- Monotherapy with a LABA, such as vilanterol, increases the risk of serious asthma-related events, such as hospitalizations, intubations, and asthma-related death. When combined with ICS, this risk does not significantly increase, compared with treatment only with an ICS. Moreover, vilanterol, like other LABAs, can lead to clinically significant cardiovascular effects in some patients, including increased blood pressure and cardiac arrhythmias.
- A case report also indicated that inhaled LAMAs, such as umeclidinium, may be linked to mental health disorders (including aggressive behavior and suicidal thoughts), especially in older adults. [ref 7]

Trelegy Ellipta for the maintenance treatment of COPD

All three components of Trelegy Ellipta are approved for the treatment of COPD, either as a component of a dual combination product or as monotherapy.[8] For the approval of Trelegy Ellipta, its efficacy was assessed in three clinical trials. [ref 9] Of those, two 12-week randomized, double blind trials found that the lung function in adult participants with COPD treated with fluticasone furoate/vilanterol as well as umeclidinium was significantly increased compared with those who received fluticasone furoate/vilanterol and placebo. The third trial, a randomized, double-blind trial with a duration of 52 weeks, found that participants treated with Trelegy Ellipta had significant improvements in lung function, significantly greater health-related quality of life, as well as significantly reduced annual rates of moderate or severe exacerbations compared with participants who received only two components, either the combination of fluticasone furoate/vilanterol or the combination of umeclidinium/vilanterol. However, treatment with all three components of Trelegy Ellipta did not significantly reduce the

annual rate of severe exacerbations compared with treatment with only fluticasone furoate/vilanterol.

The safety of the triple inhaler was assessed in three clinical trials. [ref 10] Of those, two 12-week trials found that the rate of adverse events with the addition of umeclidinium was similar to treatment with only fluticasone furoate/vilanterol. For example, the rates of headaches (4%), backpain (4%) and diarrhea (2%) were comparable in those who received fluticasone furoate/vilanterol as well as umeclidinium; compared with those who received fluticasone furoate/vilanterol plus placebo (3%, 2%, and less than 1%, respectively). However, a 52-week safety trial showed that additional adverse reactions including infections (such as upper respiratory tract infections, pneumonia, bronchitis, influenza, sinusitis, rhinitis, or urinary tract infections), oral candidiasis, joint pain, or constipation occurred among participants receiving the triple inhaler. Moreover, in this trial adjudicated on-treatment deaths due to a cardiovascular event occurred at a lower rate for those who received Trelegy Ellipta (0.54 per 100 patient-years) than those in the fluticasone furoate/vilanterol arm (0.78) or the umeclidinium/vilanterol arm (0.94).

Unfortunately, there are no adequate data from randomized controlled trials comparing the effectiveness and safety of different ICS/LABA/LAMA combinations to each other. [ref 11] However, a meta-analysis including data from 21,809 COPD patients found no significant differences across such triple combination COPD treatments for efficacy (such as risk of exacerbation), or safety outcomes (including pneumonia, cardiovascular serious adverse events, or all-cause mortality), although the researchers concluded that Trelegy Ellipta had the greatest efficacy profile amongst triple inhalers approved in the United States. [ref 12]

Similarly, an administrative claims analysis including 20,388 propensity score matched pairs of adult COPD patients initiating single inhaler triple therapy compared the safety and effectiveness of the once daily Trelegy Ellipta with that of the twice daily budesonide, glycopyrrolate, and formoterol fumarate (Breztri Aerosphere). [ref 14] The researchers found that the hazard of first moderate COPD exacerbation among new users of the twice daily combination was 7% higher and of first severe COPD exacerbation 29% higher, compared with the once daily combination, whereas the incidence of first admission to hospital with pneumonia was identical in both groups.

Another observational comparative effectiveness study, funded by the manufacturer of Trelegy Ellipta, compared Medicare fee-for-service patients with COPD who either initiated treatment with Trelegy Ellipta (n=32,312) to those who started treatment with the twice daily combination Breztri Aerosphere (n=12,230). [ref 15] The study found that patients on the once daily treatment with Trelegy Ellipta had a 12% lower rate of annualized moderate or severe exacerbations, compared with those who received the twice daily combination. At 12 months after treatment initiation patients on Trelegy Elipta also had significantly lower risks of moderate to severe exacerbations (10%) and all-cause mortality (11%), compared with those treated with Breztri Aerosphere.

Trelegy Ellipta for the maintenance treatment of asthma in patients aged 18 years and older

For approval, the efficacy and safety of Trelegy Ellipta was evaluated in one randomized, double blind trial in adult participants whose asthma was inadequately controlled with an ICS/LABA combination treatment. [ref 16] The trial, which lasted 24-52 weeks, showed that treatment with Trelegy Ellipta led to statistically significant improvements in lung function, compared with treatment only with fluticasone furoate/vilanterol. Health-related quality of life measures was in favor of Trelegy Ellipta; however, the average annualized rate of exacerbation (0.31) was the same for participants on either combination.

Adverse reactions were comparable between Trelegy Ellipta and treatment only with fluticasone furoate/vilanterol. [ref 17] For example, headaches occurred for 5% receiving high dose and 9% receiving low dose Trelegy Ellipta, compared with 6% and 7% in those treated with high and low dose fluticasone furoate/vilanterol. Other common adverse reactions included infections (such as pharyngitis/nasopharyngitis, (viral) upper respiratory tract infections, bronchitis, (viral) respiratory tract infections, sinusitis, rhinitis, urinary tract infections, or influenza), and back pain.

However, the comparative efficacy of various triple therapies for asthma is difficult to assess. [ref 18] A double-blind, randomized study, funded by the manufacturer of Trelegy Ellipta, compared 2,439 participants with inadequately controlled asthma who either received the components of Trelegy Ellipta or only fluticasone furoate/vilanterol. [ref 19] The study found that while the addition of umeclidinium to the treatment improved lung function, it did not lead to significant reductions in moderate or severe exacerbations. The incidence of adverse events, including serious adverse events, however, was comparable across the different treatment groups.

Moreover, a retrospective cohort study, also funded by the manufacturer of Trelegy Ellipta, found that Trelegy Ellipta was associated with significantly higher adherence measured as proportion of days covered (0.68) than therapy with multiple-inhaler triple therapy (0.59). [ref 20] However, adherence rates were relatively low, even though one of the touted advantages of a single combined inhaler is its convenience. For example, after 12 months of treatment, only 25.9% of patients using the single inhaler persisted with treatment, compared with 15.1% of those using multiple-inhaler triple therapy.

3b. **Additional materials for Question 52c** (e.g., citations; 0/at least 10,000 characters)

Enter text here (Q52c citations) →→

1. Food and Drug Administration. Clinical review for application number 209482Orig1s000. Trelegy Ellipta. August 24, 2017. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209482Orig1s000MedR.pdf. Accessed February 27, 2025.
2. GlaxoSmithKline. Label: fluticasone furoate, umeclidinium, and vilanterol (Trelegy Ellipta). June 2023.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/209482s018lbl.pdf. Accessed February 27, 2025.

3. Mannino D, Weng S, Germain G, et al. Comparative effectiveness of fluticasone furoate/umeclidinium/vilanterol and budesonide/glycopyrrolate/formoterol fumarate among US patients with chronic obstructive pulmonary disease. *Adv Ther*. 2025 Feb;42(2):1131-1146.
4. Rogliani P, Ora J, Cavalli F, Cazzola M, Calzetta L. Comparing the efficacy and safety profile of triple fixed-dose combinations in COPD: A meta-analysis and IBiS score. *J Clin Med.* 2022 Aug 1;11(15):4491.
5. Braido F, Vlachaki I, Nikolaidis GF, et al. Single inhaler with beclometasone, formoterol, and glycopyrronium versus triple therapies in adults with uncontrolled asthma: a systematic review and meta-analysis. *Sci Rep*. 2025 Feb 4;15(1):4191.
6. GlaxoSmithKline. Label: fluticasone furoate, umeclidinium, and vilanterol (Trelegy Ellipta). June 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/209482s018lbl.pdf. Accessed February 27, 2025.
7. Inhaled antimuscarinic drugs: mental health disorders. *Prescrire Int*. November 2024; 33(264): 277.
8. Food and Drug Administration. Clinical review for application number 209482Orig1s000. Trelegy Ellipta. August 24, 2017. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209482Orig1s000MedR.pdf. Accessed February 27, 2025.
9. GlaxoSmithKline. Label: fluticasone furoate, umeclidinium, and vilanterol (Trelegy Ellipta). June 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/209482s018lbl.pdf. Accessed February 27, 2025.
10. GlaxoSmithKline. Label: fluticasone furoate, umeclidinium, and vilanterol (Trelegy Ellipta). June 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/209482s018lbl.pdf. Accessed February 27, 2025.
11. Rogliani P, Ora J, Cavalli F, Cazzola M, Calzetta L. Comparing the efficacy and safety profile of triple fixed-dose combinations in COPD: A meta-analysis and IBiS score. *J Clin Med.* 2022 Aug 1;11(15):4491.
12. Rogliani P, Ora J, Cavalli F, Cazzola M, Calzetta L. Comparing the efficacy and safety profile of triple fixed-dose combinations in COPD: A meta-analysis and IBiS score. *J Clin Med.* 2022 Aug 1;11(15):4491.
13. Feldman WB, Suissa S, Kesselheim AS, et al. Comparative effectiveness and safety of single inhaler triple therapies for chronic obstructive pulmonary disease: new user cohort study. *BMJ*. 2024 Dec 30;387:e080409.
14. Mannino D, Weng S, Germain G, et al. Comparative effectiveness of fluticasone furoate/umeclidinium/vilanterol and budesonide/glycopyrrolate/formoterol fumarate among US patients with chronic obstructive pulmonary disease. *Adv Ther*. 2025 Feb;42(2):1131-1146.

15. GlaxoSmithKline. Label: fluticasone furoate, umeclidinium, and vilanterol (Trelegy Ellipta). June 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/209482s018lbl.pdf. Accessed February 27, 2025.
16. GlaxoSmithKline. Label: fluticasone furoate, umeclidinium, and vilanterol (Trelegy Ellipta). June 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/209482s018lbl.pdf. Accessed February 27, 2025.
17. Braido F, Vlachaki I, Nikolaidis GF, et al. Single inhaler with beclometasone, formoterol, and glycopyrronium versus triple therapies in adults with uncontrolled asthma: a systematic review and meta-analysis. *Sci Rep*. 2025 Feb 4;15(1):4191.
18. Lee LA, Bailes Z, Barnes N, et al. Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): a double-blind, randomised, phase 3A trial. *Lancet Respir Med*. 2021 Jan;9(1):69-84.
19. Busse WW, Abbott CB, Germain G, et al. Adherence and persistence to single-inhaler versus multiple-inhaler triple therapy for asthma management. *J Allergy Clin Immunol Pract*. 2022 Nov 1;10(11):2904-2913.

0a. Drug →→ linaclotide (Linzess)

0b. Author →→ Azza AbuDagga, M.H.A., Ph.D.

---

1. Question 50a: On which indication(s) (which includes off-label use(s) per the definition provided in the instructions) of the selected drug would you like to provide input? (0/6000 characters, including spaces)

Enter text here (Q50a) →→ Chronic idiopathic constipation (CIC) and irritable bowel syndrome (IBS) with constipation.

---

2. Question I51: (Potential Therapeutic Alternatives): What medications would you consider to be therapeutic alternatives for the selected drug for each indication(s)? Provide supporting rationale and citations where applicable. (0/36,000 characters)

Enter text here (Q51) →→ Dietary fiber supplements and various laxatives, such as bulk-forming (including psyllium and methylcellulose) or saline-based ones, as well as dietary modification, including gluten-free diet or low-fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP).

2b. Additional materials for Question 51 (e.g., citations; 0/at least 10,000 characters)

Enter text here (Q51 citations) →→

1. Do not use linaclotide (LINZESS) for irritable bowel syndrome or constipation. Worst Pills, Best Pills, News. January 2017. https://www.worstpills.org/newsletters/view/1079. Accessed February 27, 2025.

2. National Institute for Health and Care Management. Irritable bowel syndrome in adults: diagnosis and management. Updated April 4, 2017. https://www.nice.org.uk/guidance/cg61/resources/irritable-bowel-syndrome-in-adults-diagnosis-and-management-pdf-975562917829. Accessed February 27, 2025.

I52: (Comparative Clinical Evidence)

3. Question 52c: For the indication(s) of the selected drug, identify any relevant evidence evaluating the clinical comparative effectiveness (e.g., clinical efficacy, real-world effectiveness, or safety) of the selected drug and potential therapeutic alternatives. Relevant comparative evidence may include but is not limited to: head-to-head randomized controlled trials, pragmatic clinical trials, network meta-analyses, observational studies, and real-world evidence. Provide supporting citations. (0/36,000 characters)

Enter text here (Q52c) →→

Linaclotide is an oral, once-daily laxative closely related to an enterotoxin secreted by certain strains of Escherichia coli. It increases intestinal fluid and accelerates gastrointestinal transit. Similar to other laxatives, it does not cure the underlying cause of constipation. Public Citizen's Health Research Group has designated linaclotide as a Do Not Use drug because, as discussed below, the randomized, placebo-controlled clinical trials supporting its approval showed that its limited benefit (symptomatic relief of constipation in about one of five users) are offset by its diarrhea adverse effects (also reported in about one of five users). Moreover, the clinical significance of linaclotide's improvement in constipation symptoms is unclear. Additionally, linaclotide has other serious risks.

In 2012 the Food and Drug Administration (FDA) approved linaclotide based on evidence from four clinical trials — lasting only three to six months — that demonstrated more frequent symptomatic relief of constipation in linaclotide-treated patients than in those taking a placebo. Mainly, about 20% of IBS participants treated with linaclotide reported increased bowel movements compared with about 6% of those taking a placebo. In contrast, diarrhea was reported in nearly 20% of linaclotide users compared with 3% of those who received a placebo. Almost 10% of linaclotide users discontinued the drug because of adverse effects. Importantly, participants in these preapproval trials were asked not to change their dietary or lifestyle habits or their dosage of other constipation medications and were permitted to take the stimulant laxative bisacodyl (Dulcolax, others, and generics) as "rescue" treatment during the trials. This may have falsely inflated the observed benefit of linaclotide. In addition, in at least one of linaclotide's preapproval trials, abdominal pain and constipation recurred after linaclotide was stopped, showing the limited benefit of the drug.

Linaclotide has not been compared with other, older laxatives in clinical trials. Therefore, it is not clear whether its benefit-risk profile is better than the profile the older these drugs. For example, in 2019 Fukudo et al. reported results from an industry-funded, randomized, placebo-controlled trial that enrolled 186 Japanese participants with chronic constipation. Initially, the trial showed that 53% of participants who took linaclotide experienced higher complete spontaneous bowel movement responder rates, compared with 26% of those who took a placebo. Although this trial was extended to 52 weeks, its placebo subjects were switched to linaclotide after the fourth week, precluding the ability to compare the long-term effect of the drug, even in comparison with a placebo.

In fact, clinical guidelines by the U.K.'s National Institute for Health and Care Management do not recommend considering linaclotide for IBS patients except if they have had constipation for more than 12 months and they were not helped by the maximum or optimal tolerated doses of other laxatives. These guidelines also recommend regular follow-up of linaclotide users who have been taking linaclotide for more than three months.

The full risks of linaclotide are not known. For example, it can increase the risk of ischemic colitis, a potentially fatal inflammatory condition that develops when there is insufficient blood flow to the colon, often due to intestinal obstruction. Ischemic colitis can lead to rectal bleeding or bloody stools, as well as inflammation and perforation of the colon. In severe cases, the condition may necessitate surgery. Although an FDA medical reviewer advocated for the inclusion of ischemic colitis in the safety warning of linaclotide's labeling, such warning was not adopted by the agency. Instead, the medication guide warns against the risk for intestinal blockage and instructs patients who "develop unusual or severe stomach-area (abdomen) pain, especially [with] bright red, bloody stools or black stools that look like tar" to immediately seek emergency care.

Linaclotide's labeling also fails to disclose evidence of additional adverse gastrointestinal effects associated with the drug, including diverticulitis and related diverticular perforation and bleeding. Several patients enrolled in linaclotide's clinical trials discontinued treatment due to intestinal obstruction. Peritonitis (a potentially fatal infection of the abdominal cavity) occurred in a participant taking linaclotide in preapproval trials. In contrast, no such adverse events occurred in participants who took a placebo.

Similar to many therapeutic proteins, linaclotide can induce an immune response called "immunogenicity" in which the body reacts against the drug, rendering it less effective. Linaclotide mimics naturally occurring proteins called guanylins that are distributed throughout the body and are essential to the functioning of the heart, brain, and lungs. Thus, this immune response could hypothetically also render these natural hormones ineffective and, in turn, cause potentially serious adverse effects. Despite these safety concerns, the FDA did not require linaclotide's manufacturer to conduct immunogenicity testing before approval. Linaclotide's manufacturer convinced the FDA that linaclotide is only minimally absorbed from the intestines and, therefore, is unlikely to cause an immune reaction that could block naturally occurring guanylins in other parts of the body.

Furthermore, Public Citizen's Health Research Group is troubled that the FDA overlooked evidence from preapproval clinical trials indicating that linaclotide is associated with adverse events that suggest an immune response. These adverse effects include serious allergic reactions, including anaphylaxis (a severe, life-threatening allergic reaction) and urticaria (hives).

3b. Additional materials for Question 52c (e.g., citations; 0/at least 10,000 characters)

Enter text here (Q52c citations) →→

1. Do not use linaclotide (LINZESS) for irritable bowel syndrome or constipation. Worst Pills, Best Pills, News. January 2017. https://www.worstpills.org/newsletters/view/1079. Accessed February 27, 2025.

2. National Institute for Health and Care Management. Irritable bowel syndrome in adults: diagnosis and management. Updated April 4, 2017. https://www.nice.org.uk/guidance/cg61/resources/irritable-bowel-syndrome-in-adults-diagnosis-and-management-pdf-975562917829. Accessed February 27, 2025.

3. AbbVie. Label: linaclotide capsule (LINZESS). June 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/202811s021lbl.pdf. Accessed February 27, 2025.

4. A bacterial enterotoxin derivative with a laxative action, nothing more. Prescrire Int. 2014;23(155):285-288.

5. Linaclotide (LINZESS) for constipation. Med Lett Drugs Ther. 2012;54(1403):91-92.

6. Fukudo S, Miwa H, Nakajima A, et al. High-dose linaclotide is effective and safe in patients with chronic constipation: A phase III randomized, double-blind, placebo-controlled study with a long-term open-label extension study in Japan. Neurogastroenterol Motil. 2019;31(1):e13487.

7. Food and Drug Administration. Division director summary review for LINZESS (linaclotide) NDA 202811. August 29, 2012. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202811Orig1s000SumR.pdf. Accessed February 27, 2025.

8. Food and Drug Administration. Division director summary review for LINZESS (linaclotide) NDA 202811. August 29, 2012. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202811Orig1s000SumR.pdf. Accessed February 27, 2025.

9. Food and Drug Administration. Clinical review for LINZESS (linaclotide) NDA 202811. July 17, 2012. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202811Orig1s000MedR.pdf. Accessed February 27, 2025.

10. Sindic A. Current understanding of guanylin peptides actions. ISRN Nephrol. 2013;2013 (April 17):813648.

0a. Drug →→ linagliptin (**Tradjenta**)

0b. Author →→ Michael Abrams, M.P.H., Ph.D.

Question 50a: On which indication(s) (which includes off-label use(s) per the definition provided in the instructions) of the selected drug would you like to provide input? (0/6000 characters, *including spaces*)

Enter text here (Q50a) **→→** Glycemic control in the context of type 2 diabetes

---

Question I51: (Potential Therapeutic Alternatives): What medications would you consider to be therapeutic alternatives for the selected drug for each indication(s)? Provide supporting rationale and citations where applicable. (0/36,000 characters)

Enter text here (Q51) **→→** *UpToDate*[1] tabulates the following glucose-lower interventions, of which there are many, including therapies that do not involve the use of pharmaceuticals:

1) lifestyle changes (nutrition and exercise)
2) metformin
3) insulin
4) GLP-1 agonists
5) GIP agonists
6) SGLT-2 inhibitors
7) sulfonylureas
8) glinides
9) pioglitazone
10) DPP-4 inhibitors (including linagliptin and sitagliptin)
11) alpha-glucosidase inhibitors
12) bariatric surgery

Additional materials for Question 51 (e.g., citations; 0/at least 10,000 characters)

Enter text here (Q51 citations) **→→**

1. Wexler DJ. Management of persistent hyperglycemia in type 2 diabetes mellitus. *UpToDate*. January 28, 2025.

I52: (Comparative Clinical Evidence)

1. Question 52c: For the indication(s) of the selected drug, identify any relevant evidence evaluating the clinical comparative effectiveness (e.g., clinical efficacy, real-world effectiveness, or safety) of the selected drug and potential therapeutic alternatives. Relevant comparative evidence may include but is not limited to: head-to-head randomized controlled trials, pragmatic clinical trials, network meta-analyses, observational studies, and real-world evidence. Provide supporting citations. (0/36,000 characters)

Enter text here (Q52c) →→ In March 2023, Public Citizen's Health Research Group continued the classification of all gliptins including linagliptin (TRADJENTA) and sitagliptin (JANUVIA) as "Do Not Use**,"** because the glycemic reducing benefits of such drugs do not outweigh their risks. Those risks include severe joint pain, acute pancreatitis, heart failure and severe skin reactions. [ref 1] Public Citizen's "Do Not Use" classification dates back to 2012. [ref 2]

A June 2022 systematic review and meta-analysis published in *BMJ* found that gliptin use, compared to the use of other diabetes drugs increased the risk of gallstones or gallbladder inflammation by approximately 11 additional cases per 10,000 persons-years exposed to such drugs.[ref 3] That work also showed that compared to patients taking flozins (sodium-glucose cotransporter 2 (SGLT-2) inhibitors, for example, empagliflozin [JARDIANCE]), those taking gliptins had a 55% higher relative risk of gallbladder inflammation and a 31% similarly-heightened risk of developing gallstones. A May 2023 brief from *Prescrire International* reviewed this same study and concluded that: "Gliptins have not proven efficacy against the complications of diabetes and have a burdensome adverse effect profile making them drugs to avoid." [ref 4]

Gliptins, also known as dipeptidyl peptidase-4 (DPP-4) inhibitors, have not demonstrated efficacy to change the risk of major adverse cardiovascular events, hospitalization for heart failure or progression of chronic kidney diseases among patients with type 2 diabetes who have cardiovascular disease. [ref 5] Based on such data *The Medical Letter* notes DPP-4 inhibitors are only preferred to control glycemic levels when there is a need to minimize the risk of hypoglycemia. Other diabetes drugs that also mitigate the risk of hypoglycemia are GLP-1 agonists (for example, semaglutide), SGLT-2 inhibitors or pioglitazone. *The Medical Letter* further notes that fatal hepatic failure may result from gliptin use.

Authoritative medical consensus (for example, among *UpToDate* authors) points to diet and exercise as first-line responses to elevated blood sugar. If those lifestyle methods fail, then metformin monotherapy is the next recommended approach; the use of insulin or other glycemic regulators would be used later if necessary.[ref 6] *UpToDate* authors do "prefer linagliptin" as one of several options for patients with chronic kidney disease not requiring dialysis who need glycemic control not afforded by metformin. Other options include GLP-1 agonists, sulfonylureas or repaglinide.

For serious challenges with glycemic control *UpToDate* authors note that bariatric surgery is highly impactful and seemingly more so than existing pharmacologic interventions. For example, one prospective observational study with 316 participants found hyperglycemia remission (defined as at least 3 months of HbA1c < 6.5%) rates of 38% three years after surgery compared

to 2.6% of patients only treated with medical/lifestyle approaches that included pharmacologic interventions. [ref 7]

Per linagliptin's 2023 product label, [ref 8] pooled data from 14 placebo-controlled trials revealed three adverse reactions that occurred in at least 2% of patients receiving linagliptin and more than in patients receiving placebo: nasopharyngitis 7.0% versus 6.1%, diarrhea 3.3% versus 3.0%, and cough 2.1% versus 1.4%. These pooled trial results involved 3,625 participants on linagliptin and 2,176 participants on placebo. All patients were diagnosed with type 2 diabetes and were followed up for 18 to 24 weeks of treatment. In sub-analyses, urinary tract infection was markedly more common (3.0% versus 0%) when linagliptin was used in combination with other antidiabetic medications, and when the other drug was pioglitazone; hyperlipidemia also was markedly increased compared to placebo (2.7% versus 0.8%). When the other drug was basal insulin, constipation was observed to be more prevalent (2.1% versus 1%).

A separate comparative study involved 104-week follow-up, 776 patients on linagliptin and 776 patient on glimepiride (a sulfonylurea); all patients in this trial also were on metformin.[ref 8] Notable adverse events that were more prevalent in the linagliptin group were back pain (9.1% versus 8.4%), arthralgia (8.1% versus 6.1%), upper respiratory tract infections (8.0% versus 7.6%, headache (6.4% versus 5.2%), cough (6.1% versus 4.9%), and pain in extremities (5.3% versus 3.9%).

Monotherapy with linagliptin in 18- and 24-week double blind studies with type 2 diabetes (n=730 patients) showed the medication to be effective in lowering HbA1c levels (approximately 0.6% on average). [ref 8] Although the drug label summarizes several trials that generally show when a treatment regimen combines linagliptin with other drugs, the HbA1c effect is increased by similar amounts (~0.6%), some of these same trials also show that, head-to-head, monotherapy with metformin is equivalent or superior to linagliptin. For example, in a 24-week randomized trial that compared treatment with 5 mg of linagliptin in 135 participants with type 2 diabetes to 141 participants on 500 mg of metformin, the former group saw HbA1c levels drop an average of 0.6% while the latter group drop was 0.8% (label, Table 7). Moreover, at 24 weeks an estimated 14% of the linagliptin group achieved HBA1c levels below 7%, compared to 26% achieving comparable results in the metformin group.

A 104-week non-inferiority double-blinded clinical trial comparing glimepiride (3 mg) treatment (n=755) to linagliptin (5 mg) treatment (n=764) showed slight advantages for glimepiride at 52- and 104-weeks, averaging a -0.2% change in HbA1c. The trial also found a statistically-significant advantage for glimepiride in lowering fasting plasm glucose (label, Tabel 8). [ref 8]

Finally, two substantial clinical studies (acronyms: CARMELINA, CAROLINA) showed that linagliptin was neither superior to placebo nor glimepiride for the achievement of desirable cardiovascular outcomes.[ref 8]

CARMELINA trial was a double-blind trial with 3,494 participants on linagliptin and 3,485 participants on placebo followed for a median duration of 2.2 years. Specific outcomes assessed were cardiovascular deaths, non-fatal myocardial infarctions and non-fatal stroke. None of these outcomes differed by treatment; calculated hazard ratios ranging from 0.88 to 0.96 with 95%

confidence intervals ranging from 0.63 to 1.45 (label, Table 13). The CAROLINA trial was also designed to compare the cardiovascular effectiveness of linagliptin and glimepiride, it included 3,023 participants randomized to linagliptin and 3,010 randomized to glimepiride. Hazard ratios calculated in the CAROLINA trials for cardiovascular death, non-fatal myocardial infarction and non-fatal stroke all show that linagliptin and glimepiride treatments were equivalent for these end point hazard ratios range from 0.87 to 1.00 with 95% confidence intervals ranging from 0.66 to 1.24 (label, Table 14).

3b. **Additional materials for Question 52c** (e.g., citations; 0/at least 10,000 characters)

Enter text here (Q52c citations) →→

1. *Worst Pills, Best Pills News*. "Do Not Use" type 2 diabetes gliptin drugs also raise risk of gallbladder inflammation. March, 2023. https://www.worstpills.org/newsletters/view/1521. Accessed February 14, 2025.
2. *Worst Pills, Best Pills News*. A review of the 'gliptin' diabetes drugs. March 2012. https://www.worstpills.org/newsletters/view/784. Accessed February 21, 2025.
3. He L, Wang J, Ping F, et al. Dipeptidyl peptidase-4 inhibitors and gallbladder or biliary disease in type 2 diabetes: systematic review and pairwise and network meta-analysis of randomized controlled trials. *BMJ*. 2022;377:e068882.
4. *Prescrire International*. Gliptins and GLP-1 agonists: gallstones and cholecystitis. Translated from *Rev Prescrire* May 2023 Volume 43, Number 475, page 354.
5. *The Medical Letter on Drugs and Therapeutics*. Drugs for type 2 diabetes. Volume 64, Issue 1663, page 177. November 14, 2022.
6. Wexler DJ. Management of persistent hyperglycemia in type 2 diabetes mellitus. *UpToDate*. January 28, 2025.
7. Kirwan JP, Courcoulas AP, Cummings DE, et al. Diabetes remission in the alliance of randomized trials of medicine Versus metabolic surgery in type 2 diabetes (ARMMS-T2D). *Diabetes Care* 2022; 45:1574.
8. Boehringer Ingelheim. Label: linagliptin (TRADJENTA). June 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/201280s027lbl.pdf. Accessed February 21, 2025.

0a. Drug →→ Janumet (metformin plus sitagliptin)

0b. Author →→ Michael Abrams, M.P.H., Ph.D.

---

2. Question 50a: On which indication(s) (which includes off-label use(s) per the definition provided in the instructions) of the selected drug would you like to provide input? (0/6000 characters, *including spaces*)

Enter text here (Q50a) →→ Glycemic control in the context of type 2 diabetes

---

3. Question I51: (Potential Therapeutic Alternatives): What medications would you consider to be therapeutic alternatives for the selected drug for each indication(s)? Provide supporting rationale and citations where applicable. (0/36,000 characters)

Enter text here (Q51) →→

1. Separate dose adjustment of metformin followed by sitagliptin or another second-line type 2 diabetes drug, with dose adjustment as needed, and depending upon the clinical presentation.

UpToDate [ref 1] specifically tabulates the following glucose-lowering interventions:

2. lifestyle changes (nutritional and exercise)
3. metformin
4. insulin
5. GLP-1 agonists
6. GIP agonists
7. SGLT-2 inhibitors
8. sulfonylureas
9. glinides
10. pioglitazone
11. DPP-4 inhibitors (including linagliptin and sitagliptin)
12. alpha-glucosidase inhibitors

Additional materials for Question 51 (e.g., citations; 0/at least 10,000 characters)

Enter text here (Q51 citations) →→

2. Wexler DJ. Management of persistent hyperglycemia in type 2 diabetes mellitus. *UpToDate*. January 28, 2025.

I52: (Comparative Clinical Evidence)

4. Question 52c: For the indication(s) of the selected drug, identify any relevant evidence evaluating the clinical comparative effectiveness (e.g., clinical efficacy, real-world effectiveness, or safety) of the selected drug and potential therapeutic alternatives. Relevant comparative evidence may include but is not limited to: head-to-head randomized controlled trials, pragmatic clinical trials, network meta-analyses, observational studies, and real-world evidence. Provide supporting citations. (0/36,000 characters)

Enter text here (Q52c) →→

Janumet is a fixed-dose combination of the two drugs, sitagliptin and metformin. Sitagliptin was approved in 2006 and is the first FDA-approved gliptin. In 2007 Public Citizen's Health Research classified sitagliptin as "Do Not Use for Seven Years," because serious adverse effects of a new drug typically become known during the first seven years on the market. In 2012 sitagliptin and other gliptins, or gliptin-combinations including Janumet, were evaluated and classified by Public Citizen as "Do Not Use" (indefinitely) because the glycemic control benefits of such drugs do not outweigh their risks.[ref 1] Those risks include severe joint pain, acute pancreatitis, heart failure, severe skin reactions and vitamin B12 deficiency. [ref 2] In 2023, Public Citizen restated the "Do Not Use" classification for gliptins after reviewing a 2022 study that confirmed the risk of gallbladder inflammation associated with this class of drugs. [ref 3]

That 2022 study was a systematic review and meta-analysis published in *BMJ*. It found that gliptin use, compared to the use of other diabetes drugs, increased the risk of gallstones or of gallbladder inflammation by approximately 11 additional cases per 10,000 persons-years exposed to such drugs. [ref 3] That work also showed that compared to patients taking flozins (sodium-glucose cotransporter 2 [SGLT-2] inhibitors; for example, empagliflozin [JARDIANCE]) those taking gliptins had a 55% higher relative risk of gallbladder inflammation and a 31% similarly-heightened risk of developing gallstones. A May 2023 brief from *Prescrire International* reviewed this same study and concluded that "Gliptins have not proven efficacy against the complications of diabetes and have a burdensome adverse effect profile making them drugs to avoid." [ref 4]

Gliptins, also known as dipeptidyl peptidase-4 (DPP-4) inhibitors, have not demonstrated efficacy to reduce the risk of major adverse cardiovascular events, hospitalization for heart failure or progression of chronic kidney diseases among patients with type 2 diabetes who have cardiovascular disease. [ref 5] Based on such data, *The Medical Letter* notes DPP-4 inhibitors are only preferred to control glycemic levels when there is a need to minimize the risk of hypoglycemia. Other diabetes drugs that also mitigate the risk of hypoglycemia are GLP-1 agonists (for example, semaglutide), SGLT-2 inhibitors or pioglitazone. *The Medical Letter* further notes that fatal hepatic failure may result from gliptin use.

Authoritative medical consensus (for example, among *UpToDate* authors) points to diet and exercise as first-line responses to elevated blood sugar. If those lifestyle methods fail, then metformin monotherapy use is the next recommended approach; the use of insulin or other drugs for glycemic control would be later, if necessary. [ref 6] *UpToDate* authors do "prefer linagliptin" as one of several options for patients with chronic kidney disease not requiring dialysis who need glycemic control not afforded by metformin. Other options include GLP-1 agonists, sulfonylureas or repaglinide.

In contrast to gliptins, Public Citizen's Health Research Group has, classified metformin as "Limited Use"— as an adjuvant therapy to diet and exercise— for glycemic control. [ref 7] The drug label for metformin includes a boxed warning for lactic acidosis, a condition that is extremely rare, but fatal about 50% of the time. Metformin should be avoided in patients with

severe kidney disease, liver disease, and cautiously used in those with other risk factors for metformin-associated lactic acidosis, including heart failure.

For serious challenges with glycemic control *UpToDate* authors note that bariatric surgery is effective and seemingly more effective than many pharmacologic interventions. For example, one prospective observational study with 316 participants found hyperglycemia remission (defined as at least 3 months of HbA1c < 6.5%) rates of 38% three years after bariatric surgery, compared to 2.6% of patients treated with medical/lifestyle approaches that included pharmacologic interventions. [ref 8]

Several randomized, placebo-controlled studies support the incremental efficacy of adding sitagliptin to metformin, effects that range from -0.4% to -0.9% reductions in HbA1c. [ref 9] However, sitagliptin's addition to metformin is not necessarily superior to the similar addition of other glycemic treatments including the sulfonylureas, such as glipizide. Specifically, a 52-week trial compared sitagliptin to glipizide as an add-on treatment for patients whose HbA1c was inadequately controlled by metformin monotherapy. In that trial, which is highlighted on the Janumet label, both groups had similar changes in HbA1c (-0.5% or -0.6%, with baseline values of 7.6% or 7.7%), and nearly identical declines of 8 points for free plasma glucose (baseline values of 164 or 168 mg/dL).

Recent head-to-head comparative effectiveness trials for Janumet and other medications for glycemic control are few. A 2024 trial directly compared empagliflozin and metformin to sitagliptin and metformin; the trial found that the drug combination containing empagliflozin was superior at reducing HbA1c. The trial involved 300 participants at a tertiary care teaching hospital in India. Patients were randomized to receive either metformin plus empagliflozin or metformin plus sitagliptin. At the three-month mark, HbA1c levels decreased significantly more from baseline in the empagliflozin group (-1.34% versus -0.65%).[ref 10]

Overall, the evidence suggests that combinations of glycemic control medications should be rarely used, and only after metformin or other monotherapies have failed. Moreover, fixed-combination products seem unnecessary given that the patient's clinician can initiate dose adjustments of each drug serially or in parallel, with full knowledge of the various benefits and risks.

3b. **Additional materials for Question 52c** (e.g., citations; 0/at least 10,000 characters)

Enter text here (Q52c citations) →→

9. *Worst Pills, Best Pills News*. "Do Not Use" type 2 diabetes gliptin drugs also raise risk of gallbladder inflammation. March 2023. https://www.worstpills.org/newsletters/view/1521. Accessed February 14, 2025.
10. *Worst Pills, Best Pills News*. A review of the 'gliptin' diabetes drugs. March 2012. https://www.worstpills.org/newsletters/view/784. Accessed February 21, 2025.

11. He L, Wang J, Ping F, et al. Dipeptidyl peptidase-4 inhibitors and gallbladder or biliary disease in type 2 diabetes: systematic review and pairwise and network meta-analysis of randomized controlled trials. *BMJ*. 2022;377:e068882.
12. *Prescrire International*. Gliptins and GLP-1 agonists: gallstones and cholecystitis. Translated from *Rev Prescrire* May 2023 Volume 43, Number 475, page 354.
13. *The Medical Letter on Drugs and Therapeutics*. Drugs for type 2 diabetes. Volume 64, Issue 1663, page 177. November 14, 2022.
14. Wexler DJ. Management of persistent hyperglycemia in type 2 diabetes mellitus. *UpToDate*. January 28, 2025.
15. *Worst Pills, Best Pills News*. "Metformin: first choice drug for type 2 diabetes." August 2028. https://www.worstpills.org/newsletters/view/1210. Accessed February 18, 2025.
16. Kirwan JP, Courcoulas AP, Cummings DE, et al. Diabetes remission in the alliance of randomized trials of medicine Versus metabolic surgery in type 2 diabetes (ARMMS-T2D). *Diabetes Care* 2022; 45:1574.
17. Merck. Label: sitagliptin and metformin (JANUMET). June 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022044s052lbl.pdf. Accessed February 21, 2022.
18. Salankar H, Rode S, Arjun C, et al. Comparative study on efficacy of empagliflozin versus sitagliptin, as an add-on therapy to metformin in type 2 diabetic patients. *J Pharm Bioallied Sci.* 2024;16(Suppl 1):S335-S338.

0a. Drug →→ Rifaximin (**Xifaxan)**

0b. Author →→ Greg Dudzik, M.D.

---

1. Question 50a: On which indication(s) (which includes off-label use(s) per the definition provided in the instructions) of the selected drug would you like to provide input? (0/6000 characters, including spaces)

Enter text here (Q50a) →→ Irritable Bowel Syndrome (IBS) with diarrhea (IBS-D)

---

2. Question I51: (Potential Therapeutic Alternatives): What medications would you consider to be therapeutic alternatives for the selected drug for each indication(s)? Provide supporting rationale and citations where applicable. (0/36,000 characters)

Enter text here (Q51) →→ Potential therapeutic alternatives for rifaximin for the treatment of Irritable Bowel Syndrome with diarrhea (IBS-D) include loperamide and bile acid sequestrants (colesevelam).[ref 1] A double-blind, placebo-controlled study examined the effects of loperamide as treatment for irritable bowel syndrome and found there was a statistically significant association with the use of loperamide with reductions in stool frequency and passage

of unformed stools. [ref 2] A double-blind, placebo-controlled study found a statistically significant association with the use of colesevelam in individuals with IBS-D and reported ease of stool passage. [ref 3]

2b. Additional materials for Question 51 (e.g., citations; 0/at least 10,000 characters)

Enter text here (Q51 citations) →→

1. The Medical Letter on Drugs and Therapeutics. Drugs for Irritable Bowel Syndrome. Med Lett Drugs Ther. 2025;67(1721):17-24.

2. Cann PA, Read NW, Holdsworth CD, Barends D. Role of loperamide and placebo in management of irritable bowel syndrome (IBS). Dig Dis Sci. 1984;29(3):239-247.

3. Odunsi-Shiyanbade ST, Camilleri M, McKinzie S, et al. Effects of chenodeoxycholate and a bile acid sequestrant, colesevelam, on intestinal transit and bowel function. Clin Gastroenterol Hepatol. 2010;8(2):159-165.

I52: (Comparative Clinical Evidence)

3. Question 52c: For the indication(s) of the selected drug, identify any relevant evidence evaluating the clinical comparative effectiveness (e.g., clinical efficacy, real-world effectiveness, or safety) of the selected drug and potential therapeutic alternatives. Relevant comparative evidence may include but is not limited to: head-to-head randomized controlled trials, pragmatic clinical trials, network meta-analyses, observational studies, and real-world evidence. Provide supporting citations. (0/36,000 characters)

Enter text here (Q52c) →→

No studies were identified comparing rifaximin to other medications for IBS-D in a head-to-head randomized control trial. A systematic review and network meta-analysis published in 2020 by Black and colleagues found that rifaximin was no better than placebo for global IBS symptoms and no better than placebo for abdominal pain. [ref 1]

3b. Additional materials for Question 52c (e.g., citations; 0/at least 10,000 characters)

Enter text here (Q52c citations) →→

1. Black CJ, Burr NE, Camilleri M, et al. Efficacy of pharmacological therapies in patients with IBS with diarrhoea or mixed stool pattern: systematic review and network meta-analysis. Gut. 2020;69(1):74-82.

---

7. Question 55: What other information or evidence do you think CMS should consider in the evaluation of the selected drug? Provide citations when applicable. (0/36,000)

Enter text here for (55) →→

In the December 2017 issue of the Worst Pills, Best Pills newsletter, Public Citizen's Health Research Group designated rifaximin as Do Not Use for the treatment of IBS-D because it offers minimal short-term benefits, and its long-term effectiveness and safety, including the potential risk of promoting antibiotic resistance, are not known.[ref 1]. Below are verbatim sections of that article:

Clinical trials

The FDA's approval of rifaximin for the treatment of IBS-D was based on evidence from three randomized clinical trials.

The first two trials, called TARGET 1 and TARGET 2, were identical. Subjects in each trial received either rifaximin or a placebo three times daily for 14 days and then were followed for 10 weeks. Slightly more subjects in the rifaximin groups than in the placebo groups reported adequate relief of symptoms during at least two of the first four weeks after treatment (41 percent versus 32 percent, respectively).[ref 2] However, symptoms recurred in many patients over the 10-week follow-up period. The FDA initially rejected approval of rifaximin, in part due to concerns that evidence from these short-term trials was "inadequate for a chronic condition." [ref 3] The agency requested that the manufacturer provide additional data to support the drug's effectiveness in IBS-D patients with recurrent symptoms.

As a result of this request, the drug's manufacturer conducted a third clinical trial called TARGET 3. This trial evaluated up to two additional 14-day treatments with rifaximin, separated by 10 weeks, in adults with IBS-D who had experienced symptomatic relief after an initial 14-day treatment with the drug but developed recurrent symptoms. [ref 4] Of the 2,579 subjects initially enrolled in the TARGET 3 trial, less than half (1,074) experienced symptomatic relief from an initial 14-day course of rifaximin, and of these, nearly two-thirds experienced recurrent symptoms. [ref 5] In these subjects with recurrent symptoms, those receiving additional treatment with rifaximin were slightly more likely to have decreased abdominal pain compared with those receiving a placebo (51 percent versus 42 percent, respectively). However, additional treatment with rifaximin did not provide improvement in diarrhea symptoms compared with placebo. In fact, the incidence of diarrhea was two times greater in subjects receiving rifaximin than in those receiving a placebo (2 percent versus 1 percent, respectively).

Serious adverse effects

Most antibiotics are used for the short-term treatment of bacterial infections, not for the prevention of recurrent symptoms due to a chronic condition such as IBS-D that has no proven underlying bacterial cause.

Similar to many antibiotics, rifaximin can alter the balance of bacteria in the intestines and may increase the risk of certain infections. [refs 6-8] For example, during the TARGET 3 trial, the incidence of influenza and bronchitis was greater in subjects taking rifaximin (2 percent and 3 percent, respectively) than in those receiving a placebo (1 percent and 2 percent, respectively). [ref 9]

The FDA-approved product labeling for rifaximin also warns about the development of antibiotic-resistant bacteria. [ref 4]

In a 2011 meeting of the FDA's Gastrointestinal Drug Advisory Committee, the majority of committee members voiced concerns about long-term, repetitive use of rifaximin for the prevention of symptoms in IBS-D patients given the risks of infections and the development of antibiotic-resistant bacteria. [ref 10]

Rifaximin, like most antibiotics, can cause Clostridium difficile (C. difficile) colitis — a potentially fatal infection of the colon. Symptoms of C. difficile colitis range from mild diarrhea to severe, bloody diarrhea and may include fever, nausea, loss of appetite and weight loss. As noted in the FDA-approved product labeling for rifaximin, C. difficile infection can occur as late as two or more months after stopping treatment with the drug. [ref 4]

Against the recommendation of the FDA's Gastrointestinal Drug Advisory Committee, [ref 10] the FDA did not require the manufacturer to conduct long-term surveillance studies for C. difficile in patients taking rifaximin for IBS-D.

Rifaximin may increase the risk of liver damage. During the TARGET 3 trial, use of rifaximin was associated with more than a two-fold greater incidence of elevated liver enzymes on blood tests — an early sign of liver toxicity — compared with use of a placebo (2 percent versus 1 percent, respectively). [ref 11]

Rifaximin may be associated with muscle pains and spasms. [ref 3] Of note, during the TARGET 3 trial, subjects taking rifaximin were three times more likely to have elevated creatine phosphokinase (CPK) blood levels compared with those receiving a placebo (3 percent versus 1 percent, respectively). [ref 11] Such CPK elevations often occur in patients who have muscle injury.

Rifaximin also is associated with serious hypersensitivity (allergic) reactions, including angioedema (the sudden swelling of the face, hands, feet and/or throat) and anaphylaxis. [ref 4] Adverse skin reactions, including exfoliative dermatitis (inflammation and shedding of the skin over large areas of the body) have been reported in some patients.

7b. Citations for Q55 (at least 10,000 characters)

Enter text here for (55 citations) →→

1. Worst Pills, Best Pills. Rifaximin (XIFAXAN): Another Poor Choice for Treating Irritable Bowel Syndrome. Worst Pills, Best Pills Newsletter. December 2017. https://www.worstpills.org/newsletters/view/1169. Accessed February 20, 2025.

2. Pimentel M, Lembo A, Chey WD, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med. 2011;364(1):22-32.

3. Food and Drug Administration. Gastrointestinal Drugs Advisory Committee Meeting background package. November 16, 2011. https://wayback.archive-it.org/7993/20170405221559/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/UCM279643.pdf. Accessed February 20, 2025.

4. Salix Pharmaceuticals. Label: rifaximin (XIFAXAN). March 2017. https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=e2991a17-fa65-49bd-a5e3-c41f2179dd9e&type=pdf&name=e2991a17-fa65-49bd-a5e3-c41f2179dd9e. Accessed February 20, 2025.

5. Lembo A, Pimentel M, Rao SS, et al. Repeat treatment with rifaximin is safe and effective in patients with diarrhea-predominant irritable bowel syndrome. Gastroenterology. 2016;151(6):1113-1121.

6. Pfeiffer JK, Virgin HW. Viral immunity. Transkingdom control of viral infection and immunity in the mammalian intestine. Science. 2016;351(6270).

7. Ferrer M, Martins dos Santos VA, Ott SJ, Moya A. Gut microbiota disturbance during antibiotic therapy: A multi-omic approach. Gut Microbes. 2014;5(1):64-70.

8. Brown RL, Clarke TB. The regulation of host defences to infection by the microbiota. Immunology. 2017;150(1):1-6.

9. ClinicalTrials.gov. NCT 01543178: Irritable Bowel Syndrome With Diarrhea (IBS-D) Rifaximin Re-Treatment Study (TARGET3). https://clinicaltrials.gov/ct2/show/results/NCT01543178?term=NCT+01543178&rank=1§=X40156#othr. Accessed February 20, 2025.

10. Food and Drug Administration. Summary minutes of the Gastrointestinal Drugs Advisory Committee Meeting. November 16, 2011. https://wayback.archive-it.org/7993/20170404152452/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/UCM283448.pdf. Accessed February 20, 2025.

11. ClinicalTrials.gov. NCT 01543178: Irritable Bowel Syndrome With Diarrhea (IBS-D) Rifaximin Re-Treatment Study (TARGET3). https://clinicaltrials.gov/ct2/show/results/NCT01543178?term=NCT+01543178&rank=1§=X40156#othr. Accessed February 20, 2025.