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Letter to Editor

# Rifaximin: One Molecule to Rule Them All?

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## Letter to Editor

The antibiotic rifaximin has been prescribed since the mid '80s to treat intestinal infections of Gram + and Gram -. Considering its effectiveness and consolidated use, in recent years rifaximin has been administered with or without scientific basis to achieve different therapeutic outcomes. In addition to the approved indications, rifaximin is routinely used for irritable bowel syndrome with diarrhoea symptoms and diverticular disease (SUDD) of various forms [1,2]. In the first case, the FDA released the recommendation to use in 2020, in this setting rifaximin is used as standard therapy to differentially diagnose IBS and other diseases [3]. On the other hand, the application for the treatment of diverticular disease remains highly controversial. The literature spends a great deal on empirically evaluating the beneficial effect on the symptoms associated with intestinal diverticula [4]. However, there is neither evidence nor real-world data sufficient to endorse the success of the therapeutic outcome. Finally, the position paper of the Italian Society of Gastroenterology and Digestive Endoscopy (SIGE), issued in 2022 agrees with the lack of effectiveness of a long term rifaximin use for the treatment of SUDD [5]. It is certainly true that rifaximin, given its physicochemical nature, is unlikely to cause adverse drug reactions, but repeated administration, continuous or cyclical, does not improve the outcomes and exposes patients to clinical risks such as the damage of the intestinal wall [6]. Following the concerning spike of prescriptions delivered in our local area, the Pharmaceutical Department undertook a deep analysis of the current uses of rifaximin by analysing the risks and possible alternatives. The most common dose regimens are presented in *Table 1* sorted by indications on label and off label as stated by the Italian Regulatory Agency (AIFA). As regard the off-label use, the table has been filled out after a narrative review of the literature. Nonetheless, the reader must be aware that the recommended dosage and duration can be tailored to the patient's needs. To establish a standard dose regimen for the off label use, we relied on the latest scientific evidence [7,8]. Rifaximin has shown a little but clinically relevant interaction with warfarin resulting in the reduction of the INR levels, this is likely due to the augmented intestinal permeability occurred in patients affected by Small Intestine Bacterial Overgrowth (SIBO) which may increase the oral bioavailability of rifaximin and therefore the induction of the CYP3A4 enzyme

**Table 1**: Therapeutic Indications of Rifaximin in Europe. Details regarding the dose regimens are retrieved from the SmPC (a), clinical practice and literature (b).

| Therapeutic Indication | Dose Regimen |
|---|---|
| **ON LABEL** | |
| Pre/post-surgery prophylaxis (a) | 1000 mg prophylaxis pre-surgery, |
| | repeat post-surgery if needed |
| Intestinal Infections (a) | 200 mg QID |
| Traveller's diarrhoea (a) | 400 mg/day for 3 days |
| Hyperammonemia (a) | 400 mg TID |
| **OFF LABEL** | |
| SUDD (b) | 400 mg BID for 7 days/month for 12 months |
| (Symptomatic Uncomplicated Diverticular Disease) | |
| IBS-D (b) | 1200 mg/day for 14 days |
| Treatment should be discontinued after 7 days (a) | |





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[9]. In other conditions, the potential induction on the CYP3A4 enzyme constitutes a mild to low concern for the healthcare team given the very low percentage of absorption of rifaximin [10]. The great effort made to limit the antibiotic resistance spreading all around the world is in contrast with the libertine prescription of rifaximin. In the most recent years, many studies have highlighted that, on the contrary with what has always been believed, the mutation of rpoβ gene has opened to the potential resistance to rifaximin carried by different pathogens such as Clostridium difficile and tuberculosis linked strains [11]. Moreover, recent evidence revealed a relationship between the difficult eradication of *Candida spp.* in immunodeficient patients treated with long term rifaximin [12]. The development of resistance or cross-resistance with other antibiotics such as rifampicin shadows the strong belief that rifaximin can be safely used with the "try and error" approach. Finally, interviewing GPs and analysing the literature, we realised that the differences between hyperammonemia and hepatic Encephalopathy (EE) is very narrow and it cannot be detected by clinicians. In this letter, it is important to stress the difference in dosage and medical product for the treatment of hyperammonemia vs EE. Low dose rifaximin is administered as the ammonium blood levels increase and to prevent the symptoms related to EE [13]. If the symptoms occur it is recommended to switch to the higher dose formulation prescribed by registered hospital specialists.

To manage and regulate the off-label use of rifaximin, the Pharmaceutical Unit of the Venetian Area undertook an analysis of the filled prescriptions released between January and June 2022 anonymously. Data were retrieved from integrated software and analysed by date and number of total tablets per patient. Thanks to this analysis, it was possible to identify multiple critical issues. Therefore, GPs were interviewed about the potential off label use of the medications. In light of the findings, the Unit supported the clinicians in the decision-making process of deprescribing throughout the interrogation of user-friendly tools and recommendations to safer prescribe the medication in the general and hospital practices in accordance with the local healthcare committee. This dynamic approach was welcomed by physicians while building a productive and dynamic interdisciplinary cooperation between doctors and pharmacists of the same trust. The outcomes will be evalu-ated with further analysis after one year from the intervention.

In conclusion, we understand that drug repositioning has multiple advantages, both economic and clinical and should be encouraged, but the safety and efficacy of the treatment, in respect to the EBM (Evidence Based Medicine), must be supported by strong evidence. The aim of the intervention is to reduce the off label and unapproved use of rifaximin and to highlight whether to conduct studies to support different indications in the patient's interest. We believe that this sort of effort should be addressed even for drugs that are now forty years old.

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