VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Travellers' diarrhoea (TD), the name given to acute infectious diarrhoea affecting travellers originating from industrialised countries and visiting developing countries, is a very frequent health problem, although non-life threatening and self-limiting in most cases. Besides diarrhoea and faecal urgency, concomitant symptoms are abdominal cramps, nausea, vomiting and general malaise, resulting in incapacitation often costing more than 10% of the total time abroad.

High-risk destinations (20-90% incidence of TD for a 2-week stay) include most part of Africa, Asia, and Latin America, and remote destinations in Eastern Europe. Intermediate-risk destinations (8-20% incidence) include South Africa, Southern Europe, Israel, Japan, Caribbean, Argentina and Chile.

TD is associated with fecally contaminated food and beverages. Bacterial pathogens are the major cause of TD; the most frequent aetiologic agents are enterotoxinegic

Escherichia coli and enteroaggregative *Escherichia coli*, more prevalent in Africa and Latin America, meanwhile invasive pathogens including *Campilobacter jejuni*, *Shigella* spp. and *Salmonella* spp. are more common in South East Asia.

VI.2.2 Summary of treatment benefits

Four double-blind randomised studies demonstrated the clinically efficacy of rifaximin in patients with traveller's diarrhoea. Study ESID9601 (RFID9601) compared 3 dosage regimens of rifaximin (600, 1200 or 1800 mg/day) with a standard regimen of trimethoprim/sulfamethoxazole in 76 patients; study ESID9701 (RFID9701) compared rifaximin 800 mg/day to a standard regimen of ciprofloxacin in 187 patients; study ESID9802 (RFID9801) compared two doses (600 or 1200 mg/day) of rifaximin to placebo in 380 patients, and study ESID0201 (RFID3001) compared rifaximin 600 mg/day to ciprofloxacin and placebo in 399 patients.

Figure VI.2.2_1. Study ESID9601 (RFID9601): Disposition of subjects

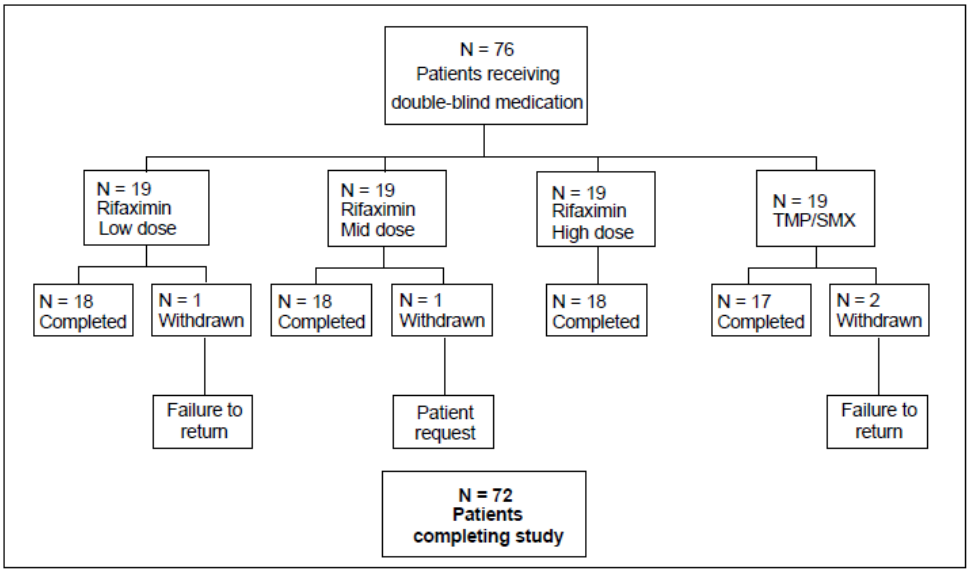


Figure VI.2.2_2. Study ESID9701 (RFID9701): Disposition of subjects

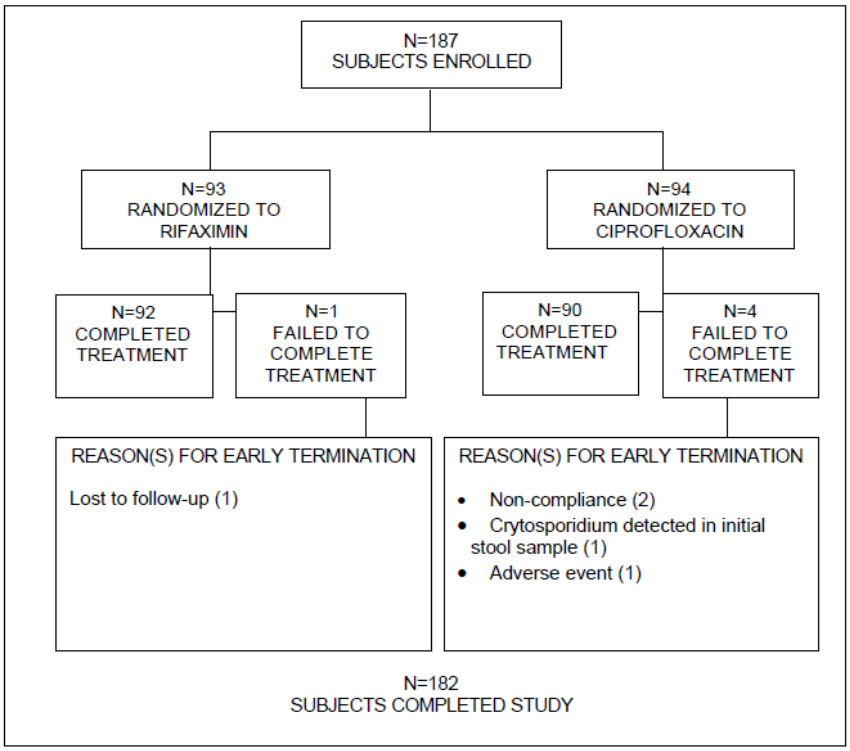


Figure VI.2.2_3. Study ESID9802 (RFID9801): Disposition of subjects

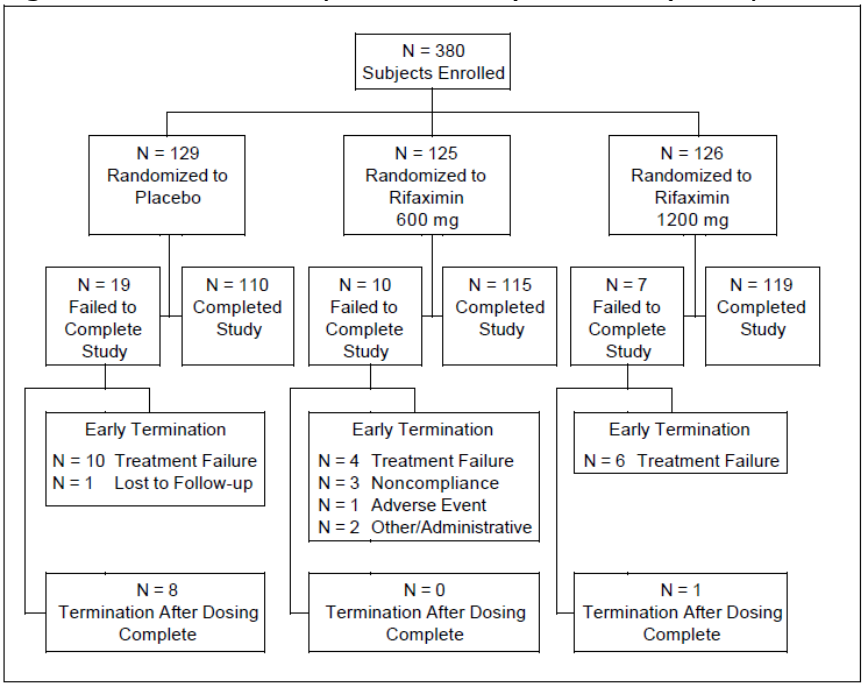
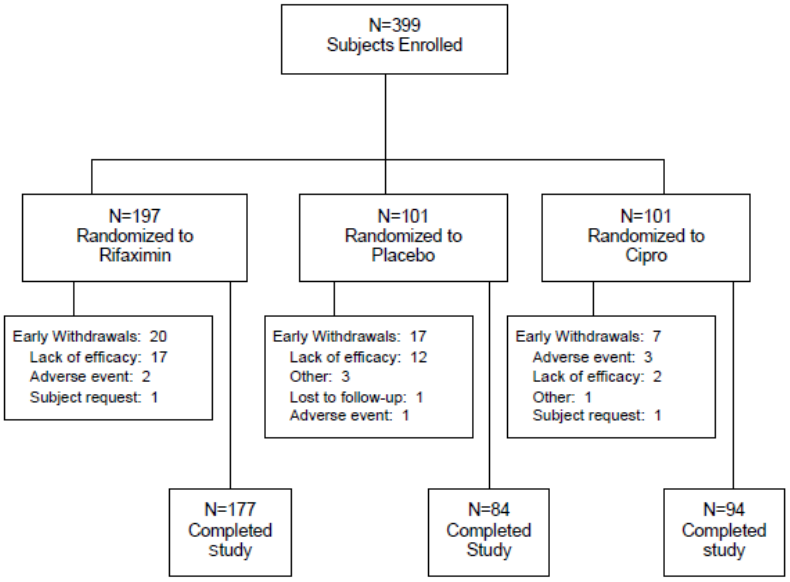


Figure VI.2.2_4. Study ESID0201 (RFID3001): Disposition of subjects



The primary efficacy endpoint for all 4 studies was the interval from the first dose of study medication to the passage of the last unformed stool (TLUS), after which wellness was declared.
In study ESID9601 (RFID9601) the median TLUS wes lowest for the rifaximin 600 mg group (26.25 h) versus rifaximin 1200 mg (40.50 h), rifaximin 1800 mg (35.00 h) and trimethoprim/sulfamethoxazole (47.00 h).
In study ESID9701 (RFID9701) the median TLUS was 25.7 h for rifaximin and 25.0 h for ciprofloxacin, demonstrating that the two treatments were equivalent.
In study ESID9802 (RFID9801) the median TLUS was 32.5 h in the rifaximin 600 mg group and 32.9 h in the rifaximin 1200 mg group versus 60 h in the placebo group.
In study ESID0201 (RFID3001) the median TLUS with rifaximin (32.0 h) was less than half than placebo (65.5 h).

VI.2.3 Unknowns relating to treatment benefits

There are not gaps in knowledge about efficacy in the target population and there is no need to perform efficacy studies post authorisation.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Clostridium Difficile infection with associated diarrhoea (CDAD)	*Clostridium difficile* associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including rifaximin.	Early detection: severe diarrhoea during or after rifaximin treatment.
Allergic Reactions	Allergic reactions have been reported after treatment with rifaximin. Even if very low quantities of the drug are absorbed in the blood, are sufficient to trigger an allergic reaction, particularly in hypersensitive subjects.	Known risk factors: patients with known allergy to: • rifaximin • similar types of antibiotics (such as rifampicin or rifabutin) • any of the other ingredients of this medicine (listed in section 6 of the PIL). Early detection: presence of reactions such as itching, hives or wheezing/shortness of breath or also swelling of the face, lips or tongue.
INR abnormalities	Cases of both increases and decreases in International Normalised Ratio (INR) were reported with a temporal association with rifaximin administration.	Closer INR monitoring and/or dose adjustment of warfarin is required during rifaximin administration.

Important potential risks

Risk	What is known
New drug-drug interactions	Broad-spectrum antibiotics administration can reduce the amount of the normal bacterial flora in the bowel, therefore the absorbed amount of others drugs concomitantly administered could change.
Potential for cross resistance to rifampicin	Subjects affected by an undiagnosed systemic bacterial infection potentially treatable with rifampicin and administered with rifaximin could present a potential cross-resistance.
Use of rifaximin for unauthorised indications (off-label use)	There is potential for off-label use in conditions other than traveller's diarrhoea; the product is already approved in a number of countries worldwide to treat gastrointestinal diseases such as intestinal infections and diarrhoea caused by diverticular disease and rifaximin 550 mg tablets are licensed the reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥ 18 years of age. In addition, clinical studies with rifaximin in irritable bowel syndrome (IBS), small intestine bacterial overgrowth (SIBO) and Crohn's disease have been published in the literature.
Use of rifaximin in the paediatric population (off-label use)	Rifaximin is proposed for the treatment of traveller's diarrhoea in adults.

Missing information

Risk	What is known
No data in the paediatric population	Rifaximin is proposed for the treatment of traveller's diarrhoea in adults. The safety and efficacy of Rifaximin in children have not been established.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

No additional risk minimisation measure are planned.

VI.2.6 Planned post authorisation development plan

No studies are planned or are conditions of the marketing authorisation.

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	05/06/2007 (RMP DLP)	**Identified Risks** • *Allergic reactions* **Potential Risks** • *Off-label use in unauthorised indications* • *Off-label use in the paediatric population*	None
1.3	31/12/2009 (RMP DLP)	**Identified Risks** • *Clostridium Difficile Associated Diarrhoea (CDAD) added as an identified risk* **Potential Risks** • *New drug-drug interactions added as potential risk*	*Clostridium Difficile Associated Diarrhoea (CDAD):* results from sponsored trials and non-sponsored studies have shown that a connection between the administration of Rifaximin and the risk of C. difficile infections can be expected. *New drug-drug interactions, as already reported in SmPC section 4.5, the potential for drug-drug interactions to occur at the level of gut transporter systems has not been evaluated and cannot be ruled out.*
2.0	20/06/2014	**Potential Risks** • *Cross-resistance to rifampicin highlighted in the potential risk section* **Missing information** • *No data in the paediatric population added*	The RMP format has been changed in accordance with the new RMP template (GVP module V). *Cross-resistance to rifampicin* was already described in the relevant RMP sections. *No data in the paediatric population* was added according to the Final Assessment Report dated 09 March 2010 of the EU work-sharing procedure for the assessment of Rifaximin paediatric data (AT/W/0001/pdWS/00)

Version	Date	Safety Concerns	Comment
3.0	30/03/2016	**Identified Risks** • *INR abnormalities moved from Potential to Identified Risks*	*INR abnormalities was already included into SmPC section 4.8.* *A*fter MHRA request dated 31/12/2015, the term has been highlighted into the identified risks.