Part VI: Summary of the risk management plan for Relafalk® 200mg modified-release tablets

This is a summary of the risk management plan (RMP) for Relafalk® 200mg modified-release tablets. The RMP details important risks of Relafalk 200mg modified-release tablets, how these risks can be minimised and how more information will be obtained about risks and uncertainties (missing information) associated with the use of the product.

Relafalk® 200mg modified-release tablets's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Relafalk® 200mg modified-release tablets should be used.

I. The medicine and what it is used for

Relafalk ® 200mg modified-release tablets is authorised in adults for the treatment of traveller's diarrhoea accompanied by symptoms like nausea, vomiting, gas/flatulence, rectal tenesmus, faecal urgency and abdominal pain or cramps without clinical signs of invasive enteritis such as fever, blood, occult blood or leucocytes in the stools (see SmPC for the full indication).
It contains rifamycin sodium as the active substance and it is given by oral route of administration.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Relafalk®, together with measures to minimise such risks and the proposed study for learning more about Relafalk®'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on medicine's packaging;
- The authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status – the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Relafalk® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Relafalk®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been

established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Bacterial resistance development
Missing information	None

II.B Summary of important risks

Important potential risk of bacterial resistance development	
Evidence for linking the risk to the medicine	The development of bacterial resistance is a major concern associated with the use of any antibacterial substance. Bacterial resistance reduces the overall efficacy of an antibiotic substance and thus has a negative impact on its benefit-risk profile. Resulting limitation of treatment options and success constitutes a serious risk to patients. The observed rate of resistance to rifamycin in the currently available literature is relatively low and similar to the reported frequencies of rifampin and rifaximin.
Risk factors and risk groups	The main risk factors for the development of bacterial resistance are the excessive/unnecessary use of antibiotics and ineffective infection control and hygiene practices frequently observed in underdeveloped countries/travel regions. Additionally, the risk of acquiring resistant bacterial strains is increased by frequent and repeat travelling in countries potentially harboring those strains independent of the intake of antibiotic substances during the stay.
Risk minimisation measures	<u>Routine risk minimisation measures</u> • Prescription-only medicine • Physicians are advised to consider official guidance on the appropriate use of antibiotics when considering prescribing Relafalk® (SmPC section 4.1).

Additional pharmacovigilance activities	Prospective Antimicrobial Surveillance Study "Frequency and susceptibility to rifamycin sodium of fecal bacteria from clinical isolates collected in regions with high prevalence of Traveller's Diarrhea" (RIB-13) See section II.C of this summary for an overview of the post-authorisation development plan

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Relafalk ® 200mg modified-release tablets.

II.C.2 Other studies in post-authorisation development plan

Study short name and title:

Frequency and antimicrobial susceptibility to rifamycin sodium of fecal bacteria from clinical isolates collected in regions with high prevalence of TD (RIB-13)

Rationale and study objectives:

The purpose of this study is to prospectively collect and perform susceptibility testing on bacterial clinical isolates derived from stool samples collected in regions with a high prevalence of TD.

Isolates will be tested against rifamycin sodium and comparators to determine the *in vitro* activity against these recent clinical isolates. Additionally, isolates of E.coli will also be molecularly characterized to determine virulence profiles for pathotype assignment.

The review period will be concluded with a trend analysis serving as basis for further characterization of the nature and severity of the identified potential risk of bacterial resistance development.