PART VI: Summary of Risk Management Plan for IMODIUM® (Loperamide Hydrochloride [HCl])

This is a summary of the Risk Management Plan (RMP) for IMODIUM (also known as IMODIUM™, IMOSEC®, FORTASEC® and ARRET™). The RMP details important risks of IMODIUM, how these risks can be minimised, and how more information will be obtained about IMODIUM's risks and uncertainties (missing information).

IMODIUM's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how IMODIUM should be used.

Important new concerns or changes to the current ones will be included in updates of IMODIUM's RMP.

I. The Medicine and What it is Used For

IMODIUM and IMODIUM Smelt are authorised for:

- Diarrhoea
- The symptomatic treatment of acute episodes of diarrhoea associated with Irritable Bowel Syndrome (IBS) in adults aged 18 years and over following initial diagnosis by a doctor.

It contains loperamide HCl as the active substance and it is given orally by tablets (2 mg) and orodispersible tablets (2 mg).

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of IMODIUM, together with measures to minimise such risks and the proposed studies for learning more about IMODIUM'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 PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the 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 (eg, 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 Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of IMODIUM is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of IMODIUM 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 IMODIUM. 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 (eg, on the long-term use of the medicine);

List of Important Risks and Missing Information	
Important identified risks	• Ileus (including paralytic ileus) • Megacolon (including toxic megacolon) • Severe skin reactions, including Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and erythema multiforme
Important potential risks	• Prolonged use masking an underlying condition requiring medical attention • Central nervous system (CNS) toxicity due to relative overdose in patients with hepatic impairment • QT prolongation and/or serious ventricular arrhythmias, including torsades de pointes (TdP) associated with abuse and misuse of loperamide
Missing information	• Use in children under 2 years of age • Use in pregnant or breastfeeding women

II.B. Summary of Important Risks

Important identified risk - Ileus (including paralytic ileus)	
Evidence for linking the risk to the medicine	Cases of ileus (including paralytic ileus) have been reported in the postmarketing setting, and are also described in the current prescribing information for loperamide.
Risk factors and risk groups	In general, there are several causes of ileus, but the most common setting for the development of ileus is the postoperative state. It is estimated that postoperative ileus occurs in approximately 50% of patients who undergo major abdominal surgery. Ileus may also develop in *Clostridium difficile* infection (CDI) where diarrhoea is a presenting symptom. Other conditions that can lead to the development of ileus include: sepsis, drugs (eg, anaesthesia, opioids, psychotropics, anticholinergics, antacids, warfarin, amitriptyline, chlorpromazine), endocrine disorders (eg, diabetes, adrenal insufficiency, hypothyroidism), and metabolic disorders (eg, low potassium, magnesium, or sodium levels; anaemia; hyposmolality).

Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.3. • SmPC Section 4.8. • SmPC Section 4.9. • PL Section 2. • PL Section 4. Additional risk minimisation measures: • None.

Important identified risk - Megacolon (including toxic megacolon)	
Evidence for linking the risk to the medicine	Cases of megacolon (including toxic megacolon) have been reported in the postmarketing setting, and are also described in the current prescribing information for loperamide.
Risk factors and risk groups	Acute megacolon may occur after orthopaedic surgery, caesarean delivery, and cardiovascular or lung surgery and can also occur in patients with other diagnoses, such as pneumonia, sepsis, myocardial infarction, or stroke. Toxic megacolon is recognised as a complication of ulcerative colitis (UC), but it may also be a complication of any number of colitides, including inflammatory, ischaemic, infectious, radiation, and pseudomembranous. Age may be considered a risk factor for toxic megacolon in that patients age 65 and older are at higher risk of developing CDI and more severe courses of the disease, including toxic megacolon. A review noted that in patients with human immunodeficiency virus (HIV) infection, toxic megacolon has been reported as a consequence of infections with cytomegalovirus, *Clostridium difficile*, Cryptosporidium, or due to Kaposi's Sarcoma-associated colitis. The authors of this review added that most patients with HIV infection and toxic megacolon were receiving antimotility drugs at the time of diagnosis, suggesting that caution is warranted when using these drugs in patients with diarrhoea.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.3. • SmPC Section 4.4. • SmPC Section 4.8. • PL Section 2. • PL Section 4. Additional risk minimisation measures: • None.

Important identified risk - Severe skin reactions, including SJS, TEN and erythema multiforme	
Evidence for linking the risk to	Cases of severe skin reactions, including SJS, TEN and erythema

the medicine	multiforme have been reported in the postmarketing setting, and are also described in the current prescribing information for loperamide.
Risk factors and risk groups	Erythema multiforme minor tends to affect adults in their 20s and 30s, although it can also affect children and adolescents, and rarely affects individuals under the age of 3 or older than 50. The mean age of patients with SJS has varied from 25 to 47 years, depending upon the series. Patients affected by TEN tend to be slightly older, with a mean reported age between 46 and 63 years. Women account for over 60% of cases. Medications are the leading trigger of SJS and TEN in both adults and children, although in children, infections are responsible for a relatively higher percentage of cases of SJS. In adults, medications cause 30% to 50% of cases of SJS and up to 80% of cases of TEN. Infections are the next most common trigger of adult SJS. Infections can also cause SJS and TEN, and there are probably other risk factors not yet identified.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.3. • SmPC Section 4.8. • PL Section 2. • PL Section 4. Additional risk minimisation measures: • None.

Important potential risk - Prolonged use masking an underlying condition requiring medical attention	
Evidence for linking the risk to the medicine	The current prescribing information describes the appropriate use of loperamide and the potential for masking underlying conditions. This safety concern was added at the request of the Medicines and Healthcare products Regulatory Agency (MHRA) as this product is available as an over-the-counter in some countries.
Risk factors and risk groups	The products are indicated to treat diarrhoea and persistent diarrhoea can be an indicator of more serious conditions that require medical attention. This includes patients with acute dysentery, acute UC, bacterial enterocolitis (e.g. due to Salmonella, Shigella, and Campylobacter), and pseudomembranous colitis associated with the use of broad-spectrum antibiotics. Prolonged use of the drug is a risk factor.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4. • PL Section 2. • PL Section 3. Additional risk minimisation measures: • None.

Important potential risk - CNS toxicity due to relative overdose in patients with hepatic impairment	
Evidence for linking the risk to the medicine	As loperamide is almost completely extracted by the liver; where it is predominantly metabolised, conjugated and excreted via the bile; there is significant first pass metabolism. Therefore, although no pharmacokinetic data are available in patients with hepatic impairment, there is a risk that when loperamide is used by patients with hepatic impairment reduced first pass metabolism may result in a relative overdose leading to CNS toxicity. Serum enzyme elevations have not been linked to therapy with loperamide, consistent with most opiates currently used. No convincing cases of idiosyncratic acute, clinically apparent liver injury have been reported. The lack of hepatotoxicity may be a result of the low doses used and the low systemic absorption.
Risk factors and risk groups	Patients with hepatic impairment have reduced first pass metabolism that may result in overdose leading to CNS toxicity. Intentional and unintentional drug overdose are risk factors for this safety concern.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2. • SmPC Section 4.4. • SmPC Section 4.8. • SmPC Section 4.9. • PL Section 2. • PL Section 3. Additional risk minimisation measures: • None.

Important potential risk - QT prolongation and/or serious ventricular arrhythmias, including TdP associated with abuse and misuse of loperamide	
Evidence for linking the risk to the medicine	Although a drug/event causal association between loperamide abuse/misuse/intentional overdose and the occurrence of QT prolongation and/or serious cardiac arrhythmias, including TdP, has not been established, cases of loperamide abuse/misuse/intentional overdose at massively high doses resulting in QT prolongation and/or serious cardiac arrhythmias, as well as cases of TdP, have been reported in some patients in the literature/postmarketing environment. Such cases, including cases with a fatal outcome, are also described in the current prescribing information for loperamide.
Risk factors and risk groups	Abuse/misuse/intentional overdose at high doses is a risk factor for the safety concern.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4. • SmPC Section 4.9. • SmPC Section 5.3.

	• PL Section 2. • PL Section 3. Additional risk minimisation measures: • None.

Missing information - Use in children under 12 years of age	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2. • SmPC Section 4.3. • SmPC Section 4.9. • PL Section 2. • PL Section 3. Additional risk minimisation measures: • None.

Missing information - Use in pregnant or breastfeeding women	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.6. • SmPC Section 5.3. • PL Section 2. Additional risk minimisation measures: • None.

II.C. Postauthorisation 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 IMODIUM.

II.C.2. Other Studies in Postauthorisation Development Plan

There are no studies required for IMODIUM.