PART I PRODUCT OVERVIEW

Active substance	Racecadotril
Pharmacotherapeutic group	Other antidiarrhoeals (ATC code: A07XA04)
Name of MAH or Applicant	Sanofi
Number of medicinal products to which this RMP refers	1
Product concerned	(Tradename)
DLP for this RMP	30-Nov-2016
Version number	1.1
Date of final sign off	16-Oct-2017

PI.Table 1 Administrative information on the RMP

Part	Module/Appendix	Date last updated for submission	Version number of RMP when part/module/appendix last submitted
Part II Safety specification	Module SI Epidemiology of the indication(s) and target population	Not applicable	Not applicable
	Module SII Non-clinical part of the safety specification	Not applicable	Not applicable
	Module SIII Clinical trial exposure	Not applicable	Not applicable
	Module SIV Populations not studied in clinical trials	Not applicable	Not applicable
	Module SV Post-authorisation experience	Not applicable	Not applicable
	Module SVI Additional European Union (EU) requirements for the safety specification	Not applicable	Not applicable

PI.Table 1 (cont'd) Administrative information on the RMP

Part	Module/Appendix	Date last updated for submission	Version number of RMP when part/module/appendix last submitted
	Module SVII Identified and potential risks	Not applicable	Not applicable
	Module SVIII Summary of the safety concerns	16-Oct-2017	1.1
Part III Pharmacovigilance plan		16-Oct-2017	1.1
Part IV Plans for post-authorisation efficacy studies		Not applicable	Not applicable
Part V Risk minimisation measures		16-Oct-2017	1.1
Part VI Summary of the RMP		16-Oct-2017	1.1
Part VII Appendices	Appendix 1 Eudravigilance interface (electronic only)	Not applicable	Not applicable
	Appendix 2 Current or proposed Summary of Product Characteristics (SmPC)/Patient Information leaflet (PIL)	16-Oct-2017	1.1
	Appendix 3 Worldwide marketing status by country	Nov-2016	1.0
	Appendix 4 Synopsis of clinical trial programme	Not applicable	Not applicable
	Appendix 5 Synopsis of pharmacoepidemiological study programme	Not applicable	Not applicable

PI.Table 1 (cont'd) Administrative information on the RMP

Part	Module/Appendix	Date last updated for submission	Version number of RMP when part/module/appendix last submitted
	Appendix 6 Protocols for proposed and ongoing studies in Part III	Not applicable	Not applicable
	Appendix 7 Specific adverse event follow-up forms	Nov-2016	1.0
	Appendix 8 Protocols for studies in Part IV	Not applicable	Not applicable
	Appendix 9 Synopsis of newly available study reports in Parts III and IV	Not applicable	Not applicable
	Appendix 10 Details of proposed additional risk minimisation activities	Not applicable	Not applicable
	Appendix 11 Mock-up examples	Not applicable	Not applicable
	Appendix 12 Other supporting data	Not applicable	Not applicable

PI.Table 2 EU-QPPV and contact person

EU-QPPV name	Hadj Benzerdjeb[a]
EU-QPPV signature	The signature is provided electronically.
Contact person for this RMP	Hannelore Halfer-Wirkus
Email address or telephone number of contact person	hannelore.halfer-wirkus@sanofi.com

[a] Deputy QPPV for sign-off

PI.Table 3 Overview of versions

Version number of last agreed RMP	
Version number	Not applicable
Agreed within	Not applicable

PI.Table 4 Current RMP versions under evaluation

RMP version number	Submitted on	Submitted within
No RMP version is currently under evaluation	Not applicable	Not applicable

PI.Table 5 Racecadotril

Invented name in EEA	Vaprino
Authorisation procedure	Decentralized procedure
Brief description of the product, incl.	
Chemical class	Oral, peripherally-acting enkephalinase inhibitor (ATC code: A07XA04)
Summary mode of action	Racecadotril is an enkephalinase inhibitor that inhibits the breakdown of endogenous opioids, thus, reducing intestinal secretions. It is a prodrug, which is converted to the active metabolite thiorphan. At the molecular level racecadotril and thiorphan act by inhibiting the enzyme neutral endopeptidase (NEP), which is a membrane-metalloendopeptidase also known as enkephalinase. Acetyl-thiorphan is another active metabolite of racecadotril but yields only low potency NEP inhibition. NEP has various substrates including enkephalins (hence the name enkephalinase) but also atrial natriuretic peptide, brain natriuretic peptide, substance P, neurotensins, and neuropeptide Y. NEP inhibition can, therefore, potentially affect any of these mediators, and observed *in vivo* effects in different organ systems may not always relate to the same enzyme substrate.
Important information about its composition	Not applicable.
Indication in the EEA	
Current	Not applicable.
Proposed	Symptomatic treatment of acute diarrhoea in adults 18 years and older.
Posology and route of administration in the EEA	
Current	Not applicable.
Proposed	For oral use.

	Adults One capsule 3 times daily, preferably before main meals. On the first day of treatment, one additional capsule should be taken with the first dose, regardless of the time of day. On the first day the total daily dose should not exceed 4 capsules (400 mg). On the consecutive days the total daily dose should not exceed 3 capsules (300 mg). Treatment should be continued as long as the stool is unformed. If symptoms worsen within the first 2 days after starting treatment or have not improved within 3 days, medical advice should be sought. Long-term treatment with Racecadotril is not recommended. Special populations: Elderly: Dose adjustment is not necessary in elderly patients. Caution is required in patients with hepatic or renal impairment.
Pharmaceutical form and strength	
Current	Not applicable.
Proposed	Hard capsule, 100mg.
Country and date of first authorisation worldwide	Not applicable
Country and date of first launch worldwide	Not applicable
Country and date of first authorisation in the EEA	Not applicable
Is the product subject to additional monitoring in the EU?	No

PART I.1 ABBREVIATIONS

ATC	Anatomic Therapeutic Classification
DLP	Data Lock Point
EEA	European Economic Area
EU-QPPV	European Qualified Person Responsible for Pharmacovigilance
MAH	Marketing Authorisation Holder
MRP	Mutual Recognition Procedure
NEP	Neutral endopeptidase
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

Active substance	Racecadotril
Product concerned	(Tradename)
Name of MAH or Applicant	Sanofi
DLP for this module	30-Nov-2016
Version number of RMP when this module was last updated	1.1

SVIII.Table 1 Summary of safety concerns

Important identified risks	Skin reaction (angioedema; tongue and lip oedema; oedema mouth; eyelid oedema; face oedema; swollen tongue) Interaction with angiotensin converting enzyme inhibitors (ACEIs) (angioedema; tongue and lip oedema; oedema mouth; eyelid oedema; face oedema; swollen tongue, lymphoedema, peripheral oedema)
Important potential risks	SCARs (Stevens-Johnson syndrome; toxic epidermal necrolysis; skin exfoliation; DRESS) Anaphylactic/hypersensitivity reactions Off-label use in chronic diarrhoea Treatment of diarrhoea induced by invasive bacteria
Missing information	Patients with renal and hepatic insufficiency Pregnant or breast-feeding women

SVIII.1 ABBREVIATIONS

DLP	Data Lock Point
MAH	Marketing Authorisation Holder
RMP	Risk Management Plan

SVIII.2 REFERENCES

Not applicable.

PART III PHARMACOVIGILANCE PLAN

Active substance	Racecadotril
Product concerned	(Tradename)
Name of MAH or Applicant	Sanofi
DLP for this module	30-Nov-2016
Version number of RMP when this module was last updated	1.1

PART III.1. SAFETY CONCERNS AND OVERVIEW OF PLANNED PHARMACOVIGILANCE ACTIONS

Routine pharmacovigilance activities are performed according to the requirements set out in the guidelines on Good Pharmacovigilance Practices (GVP). A summary of the implemented pharmacovigilance system has been provided as part of the dossier submitted as application for marketing authorisation. Detailed information on the pharmacovigilance system is available in the current Pharmacovigilance System Master File (PSMF).

Safety concern	Planned action(s)
Important identified risk	
Skin reaction (angioedema; tongue and lip oedema; oedema mouth; eyelid oedema; face oedema; swollen tongue)	Routine pharmacovigilance activities
Interaction with angiotensin-converting enzyme inhibitors (ACEIs) (angioedema; tongue and lip oedema; oedema mouth; eyelid oedema; face oedema; swollen tongue; lymphoedema; peripheral oedema)	Routine pharmacovigilance activities
Important potential risk	
SCARs (Stevens-Johnson syndrome; toxic epidermal necrolysis; skin exfoliation; DRESS)	Routine pharmacovigilance activities
Anaphylactic/hypersensitivity reactions	Routine pharmacovigilance activities
Off-label use in chronic diarrhoea	Routine pharmacovigilance activities
Treatment of diarrhoea induced by invasive bacteria	Routine pharmacovigilance activities
Missing information	
Patients with renal and hepatic insufficiency	Routine pharmacovigilance activities
Pregnant or breast-feeding women	Routine pharmacovigilance activities

PART III.2. ADDITIONAL PHARMACOVIGILANCE ACTIVITIES TO ASSESS EFFECTIVENESS OF RISK MINIMISATION MEASURES

No additional pharmacovigilance activities to assess effectiveness of risk minimisation measures are deemed necessary.

PART III.3. STUDIES AND OTHER ACTIVITIES COMPLETED SINCE LAST UPDATE OF PHARMACOVIGILANCE PLAN

Not applicable.

PART III.4. DETAILS OF OUTSTANDING ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable.

PART III.3. SUMMARY OF THE PHARMACOVIGILANCE PLAN

Finished products containing racecadotril as active substance have been marketed for many decades. Therefore, the safety profile is well established and no additional pharmacovigilance practices other than routine measures are deemed necessary. All routine pharmacovigilance practices are in accordance to the current European requirements as laid down in the respective Modules of Good Pharmacovigilance Practices (GVP) issued by the EMA.

PART III.4. ABBREVIATIONS

DLP	Data Lock Point
MAH	Marketing Authorisation Holder
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

PART III.5. REFERENCES

Not applicable.

PART V RISK MINIMISATION MEASURES

Active substance	Racecadotril
Product concerned	(Tradename)
Name of MAH or Applicant	Sanofi
DLP for this module	30-Nov-2016
Version number of RMP when this module was last updated	1.1

PART V.1 RISK MINIMISATION MEASURES BY SAFETY CONCERN

PV.Table 1 Important Identified Risk: Skin reaction (angioedema; tongue and lip oedema; oedema mouth; eyelid oedema; face oedema; swollen tongue)

Objectives of the risk minimisation measures	
Routine risk minimisation measures	*(Proposed) text in SmPC* Refer to SmPC sections: 4.4 Special warnings and precautions for use 4.8 Undesirable effects *Comment* Routine risk minimisation activities are considered sufficient. *Other routine risk minimisation measures* Package leaflet. *Product is subject to additional monitoring in the EU* No
Additional risk minimisation measures	*Objective and justification why needed* Not applicable. *Proposed actions/components and rationale* Not applicable.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable.
Criteria for judging the success of the proposed risk minimisation measures	Not applicable.
Planned dates for assessment	Not applicable.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	None.

PV.Table 2 Important Identified Risk: Interaction with angiotensin converting enzyme inhibitors (ACEIs) (angioedema; tongue and lip oedema; oedema mouth; eyelid oedema; face oedema; swollen tongue; lymphoedema; peripheral oedema)

Objectives of the risk minimisation measures	
Routine risk minimisation measures	*(Proposed) text in SmPC* Refer to SmPC sections: 4.4 Special warnings and precautions for use 4.5 Interaction with other medicinal products and other forms of interaction 4.8 Undesirable effects *Comment* Routine risk minimisation activities are considered sufficient. *Other routine risk minimisation measures* Package leaflet. *Product is subject to additional monitoring in the EU* No
Additional risk minimisation measures	*Objective and justification why needed* Not applicable. *Proposed actions/components and rationale* Not applicable.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable.
Criteria for judging the success of the proposed risk minimisation measures	Not applicable.
Planned dates for assessment	Not applicable.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	None.

PV.Table 3 Important Potential Risk: SCARs (Stevens-Johnson syndrome; toxic epidermal necrolysis; skin exfoliation; DRESS)

Objectives of the risk minimisation measures	
Routine risk minimisation measures	*(Proposed) text in SmPC* Refer to SmPC section: 4.4 Special warnings and precautions for use

	4.8 Undesirable effects *Comment* Routine risk minimisation activities are considered sufficient. *Other routine risk minimisation measures* Package leaflet. *Product is subject to additional monitoring in the EU* No
Additional risk minimisation measures	*Objective and justification why needed* Not applicable. *Proposed actions/components and rationale* Not applicable.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable.
Criteria for judging the success of the proposed risk minimisation measures	Not applicable.
Planned dates for assessment	Not applicable.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	None.

PV.Table 4 Important Potential Risk: Anaphylactic/hypersensitivity reactions

Objectives of the risk minimisation measures	
Routine risk minimisation measures	*(Proposed) text in SmPC* Refer to SmPC sections: 4.3 Contraindications 4.4 Special warnings and precautions for use 4.8 Undesirable effects *Comment* Routine risk minimisation activities are considered sufficient. *Other routine risk minimisation measures* Package leaflet. *Product is subject to additional monitoring in the EU* No
Additional risk minimisation measures	*Objective and justification why needed* Not applicable. *Proposed actions/components and rationale*

	Not applicable.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable.
Criteria for judging the success of the proposed risk minimisation measures	Not applicable.
Planned dates for assessment	Not applicable.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	None.

PV.Table 5 Important Potential Risk: Off-label use in chronic diarrhoea

Objectives of the risk minimisation measures	
Routine risk minimisation measures	*(Proposed) text in SmPC* Refer to SmPC section: 4.2 Posology and method of administration 4.4 Special warnings and precautions for use *Comment* Routine risk minimisation activities are considered sufficient. *Other routine risk minimisation measures* Package leaflet. *Product is subject to additional monitoring in the EU* No
Additional risk minimisation measures	*Objective and justification why needed* Not applicable. *Proposed actions/components and rationale* Not applicable.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable.
Criteria for judging the success of the proposed risk minimisation measures	Not applicable.
Planned dates for assessment	Not applicable.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	None.

PV.Table 6 Important Potential Risk: Treatment of diarrhoea induced by invasive bacteria

Objectives of the risk minimisation measures	
Routine risk minimisation measures	*(Proposed) text in SmPC* Refer to SmPC section: 4.4 Special warnings and precautions for use *Comment* Routine risk minimisation activities are considered sufficient. *Other routine risk minimisation measures* Package leaflet. *Product is subject to additional monitoring in the EU* No
Additional risk minimisation measures	*Objective and justification why needed* Not applicable. *Proposed actions/components and rationale* Not applicable.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable.
Criteria for judging the success of the proposed risk minimisation measures	Not applicable.
Planned dates for assessment	Not applicable.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	None.

PV.Table 7 Missing Information: Patients with renal and hepatic insufficiency

Objectives of the risk minimisation measures	
Routine risk minimisation measures	*(Proposed) text in SmPC* Refer to SmPC sections: 4.2 Posology and method of administration 4.4. Special warnings and precautions for use 5.2 Pharmacokinetic properties *Comment* Routine risk minimisation activities are considered sufficient. *Other routine risk minimisation measures*

	Package leaflet. *Product is subject to additional monitoring in the EU* No
Additional risk minimisation measures	*Objective and justification why needed* Not applicable. *Proposed actions/components and rationale* Not applicable.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable.
Criteria for judging the success of the proposed risk minimisation measures	Not applicable.
Planned dates for assessment	Not applicable.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	None.

PV.Table 8 Missing Information: Pregnant or breast-feeding women

Objectives of the risk minimisation measures	
Routine risk minimisation measures	*(Proposed) text in SmPC* Refer to SmPC sections: 4.6 Fertility, pregnancy and lactation 5.3 Preclinical safety data *Comment* Routine risk minimisation activities are considered sufficient. *Other routine risk minimisation measures* Package leaflet. *Product is subject to additional monitoring in the EU* No
Additional risk minimisation measures	*Objective and justification why needed* Not applicable. *Proposed actions/components and rationale* Not applicable.
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable.
Criteria for judging the success of the proposed risk minimisation measures	Not applicable.

Planned dates for assessment	Not applicable.
Results of effectiveness measurement	Not applicable.
Impact of risk minimisation	Not applicable.
Comment	None.

PART V.2 RISK MINIMISATION MEASURE FAILURE

Not applicable.

Part V.2.1 Analysis of risk minimisation measure(s) failure

Not applicable.

Part V.2.2 Revised proposal for risk minimisation

Not applicable.

PART V.3 SUMMARY TABLE OF RISK MINIMISATION MEASURES

PV.Table 9 Summary of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risk: Skin reaction (angioedema, tongue and lip oedema; oedema mouth; eyelid oedema; face oedema, swollen tongue)	SmPC sections: 4.4 Special warnings and precautions for use 4.8 Undesirable effects	Not applicable
Important Identified Risk: Interaction with angiotensin converting enzyme inhibitors (ACEIs) (angioedema, tongue and lip oedema; oedema mouth; eyelid oedema; face oedema, swollen tongue, lymphoedema, peripheral oedema)	SmPC sections: 4.4 Special warnings and precautions for use 4.5 Interaction with other medicinal products and other forms of interaction 4.8 Undesirable effects	Not applicable
Important Potential Risk: SCARs (Stevens-Johnson syndrome, toxic epidermal necrolysis, skin exfoliation, DRESS)	SmPC sections: 4.4 Special warnings and precautions for use 4.8 Undesirable effects	Not applicable
Important Potential Risk: Anaphylactic/hypersensitivity reactions	SmPC sections: 4.3 Contraindications 4.4 Special warnings and precautions for use 4.8 Undesirable effects	Not applicable
Important Potential Risk: Off-label use in chronic diarrhoea	SmPC sections: 4.2 Posology and method of administration 4.4 Special warnings and precautions for use	Not applicable
Important Potential Risk: Treatment of diarrhoea induced by invasive bacteria	SmPC section: 4.4 Special warnings and precautions for use	Not applicable
Missing Information: Patients with renal and hepatic insufficiency	SmPC sections: 4.2 Posology and method of administration 4.4. Special warnings and precautions for use 5.2 Pharmacokinetic properties	Not applicable
Missing Information: Pregnant or breast-feeding women	SmPC sections: 4.6 Fertility, pregnancy and lactation 5.3 Preclinical safety data	Not applicable

PART V.4 ABBREVIATIONS

DLP	Data Lock Point
MAH	Marketing Authorisation Holder
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

PART V.5 REFERENCES

Not applicable.

PART VI SUMMARY OF THE ACTIVITIES IN THE RISK MANAGEMENT PLAN BY PRODUCT

Active substance	Racecadotril
Product concerned	(Tradename)
Name of MAH or Applicant	Sanofi
DLP for this module	30-Nov-2016
Version number of RMP when this module was last updated	1.1

PART VI.1 ELEMENTS FOR SUMMARY TABLES IN THE EUROPEAN PUBLIC ASSESSMENT REPORT

PVI.Table 1 Summary table of safety concerns

Important identified risks	Skin reaction (angioedema; tongue and lip oedema; oedema mouth; eyelid oedema; face oedema; swollen tongue) Interaction with angiotensin converting enzyme inhibitors (ACEIs) (angioedema; tongue and lip oedema; oedema mouth; eyelid oedema; face oedema; swollen tongue; lymphoedema; peripheral oedema)
Important potential risks	SCARs (Stevens-Johnson syndrome; toxic epidermal necrolysis; skin exfoliation; DRESS) Anaphylactic/hypersensitivity reactions Off-label use in chronic diarrhoea Treatment of diarrhoea induced by invasive bacteria
Missing information	Patients with renal and hepatic insufficiency Pregnant or breast-feeding women

PVI.Table 2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable.

PVI.Table 3 Summary of Post-authorisation efficacy development plan

Not applicable.

PVI.Table 4 Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risk: Skin reaction (angioedema; tongue and lip oedema; oedema mouth; eyelid oedema; face oedema; swollen tongue)	SmPC sections: 4.4 Special warnings and precautions for use 4.8 Undesirable effects	Not applicable
Important Identified Risk: Interaction with angiotensin converting enzyme inhibitors (ACEIs) (angioedema; tongue and lip oedema; oedema mouth; eyelid oedema; face oedema; swollen tongue; lymphoedema; peripheral oedema)	SmPC sections: 4.4 Special warnings and precautions for use 4.5 Interaction with other medicinal products and other forms of interaction 4.8 Undesirable effects	Not applicable
Important Potential Risk: SCARs (Stevens-Johnson syndrome; toxic epidermal necrolysis; skin exfoliation; DRESS)	SmPC sections: 4.4 Special warnings and precautions for use 4.8 Undesirable effects	Not applicable
Important Potential Risk: Anaphylactic/hypersensitivity reactions	SmPC sections: 4.3 Contraindications 4.4 Special warnings and precautions for use 4.8 Undesirable effects	Not applicable
Important Potential Risk: Off-label use in chronic diarrhoea	SmPC sections: 4.2 Posology and method of administration 4.4 Special warnings and precautions for use	Not applicable
Important Potential Risk: Treatment of diarrhoea induced by invasive bacteria	SmPC section: 4.4 Special warnings and precautions for use	Not applicable
Missing Information: Patients with renal and hepatic insufficiency	SmPC sections: 4.2 Posology and method of administration 4.4. Special warnings and precautions for use 5.2 Pharmacokinetic properties	Not applicable
Missing Information: Pregnant or breast-feeding women	SmPC sections: 4.6 Fertility, pregnancy and lactation 5.3 Preclinical safety data	Not applicable

PART VI.2 ELEMENTS FOR A PUBLIC SUMMARY

Part VI.2.1 Overview of disease epidemiology

Diarrhoea is a very common disorder worldwide. In the case of 'acute' diarrhoea, it may occur suddenly and, generally, lasts for a short time only. Gut infections (gastroenteritis) are the most frequent cause of acute diarrhoea. The usual causes of acute diarrhoea in Europe are bacteria and viruses. Prominent symptoms associated with diarrhoea are frequent and watery stools, abdominal (tummy) pain, nausea, vomiting and fever. Common complications are dehydration and electrolyte (salts, e.g. potassium) loss in the diarrhoea, especially so in children and elderly patients.

Mild cases of acute diarrhoea can be treated with attention to adequate fluid intake and nutrition. The priority when treating acute diarrhoea is the prevention or reversal of fluid and electrolyte loss. The main treatment for both adults and children with acute diarrhoea is to have lots to drink, which will help to stop dehydration.

Part VI.2.2 Summary of treatment benefits

Racecadotril is an anti-diarrhoeal medication for the treatment of acute diarrhoea. It works purely in the intestine where it decreases the excess loss of water and electrolytes (salts) into the gut. This, in turn, reduces the symptoms of diarrhoea and reduces the risk of dehydration. Racecadotril does not cause abdominal bloating or constipation, because neither gut motility nor basal secretion is altered.

A 2014 analysis of clinical studies (669 patients, with 282 patients in the dummy pill (placebo) group) comparing the effectiveness of racecadotril against placebo in the treatment of acute diarrhoea in adults showed that racecadotril was significantly more effective than placebo in reducing the duration and number of episodes of diarrhoea.

Another 2014 analysis of 12 clinical studies, involving 2,619 patients, comparing the effectiveness of racecadotril against either loperamide (another anti-diarrhoeal medication) or placebo in the treatment of acute diarrhoea in adults showed that diarrhoea duration was significantly shorter in those patients being treated with racecadotril compared to placebo. The number of patients having recovered from the diarrhoea at any time of the treatment period was 65% higher with racecadotril as compared to placebo. Diarrhoea duration was similar between racecadotril treated patients and loperamide treated patients.

Part VI.2.3 Unknowns relating to treatment benefits

Limited information is available for the elderly population. The available information suggests that racecadotril effects and function are similar to those in younger adults.

Evidence is lacking for the racecadotril use in patients with chronic diarrhoea, or poor kidney or liver function. These patients should be treated with caution.

Part VI.2.4 Summary of safety concerns

PVI.Table 5 Important identified risks

Risk	What is known	Preventability
Skin reaction (angioedema; tongue and lip oedema; oedema mouth; eyelid oedema; face oedema; swollen tongue)	The occurrence of skin reactions has been reported with the use of racecadotril. These are in most cases mild and do not require treatment but in some cases they can be severe, even life-threatening. Association with racecadotril cannot be fully ruled out. When experiencing severe skin reactions (e.g. progressive skin rash often with blisters or mucosal lesions), the treatment has to be stopped immediately and medical advice should be sought.	Angioedema of the face, extremities, lips, mucous membranes may occur. Where there is angioedema associated with upper airway obstruction, such as tongue, glottis and/or larynx, emergency therapy should be administered promptly. Treatment should be discontinued and the patient should be under close medical supervision with appropriate monitoring initiated and continued until complete and sustained resolution of symptoms has occurred.
Interaction with angiotensin converting enzyme inhibitors (ACEIs) (angioedema; tongue and lip oedema; oedema mouth; eyelid oedema; face oedema; swollen tongue; lymphoedema; peripheral oedema)	Concomitant use of racecadotril and ACE inhibitors may increase the risk of angioedema. Hence, a careful benefit-risk assessment is needed before initiating treatment with racecadotril in patients on ACE inhibitors.	Angioedema of the face, extremities, lips, mucous membranes may occur. Where there is angioedema associated with upper airway obstruction, such as tongue, glottis and/or larynx, emergency therapy should be administered promptly. Treatment should be discontinued and the patient should be under close medical supervision with appropriate monitoring initiated and continued until complete and sustained resolution of symptoms has occurred.

Important potential risks

Risk	What is known (including reason why it is considered a potential risk)
SCARs (Stevens-Johnson syndrome, toxic epidermal necrolysis, skin exfoliation, DRESS)	Occurrence of skin reactions has been reported with the use of the product. These are in most cases mild and do not require treatment but in some cases they can be severe, even life-threatening. Association with racecadotril cannot be fully excluded. When experiencing severe skin reactions (e.g. progressive skin rash often with blisters or mucosal lesions), the treatment has to be stopped immediately and medical advice should be sought.
Anaphylactic/hypersensitivity reactions	It has been reported in patients with racecadotril. This may occur at any time during therapy.
Off-label use in chronic diarrhoea	Chronic diarrhoea has not been sufficiently studied with racecadotril. In cases of chronic diarrhoea, a medical doctor should be consulted.
Treatment of diarrhoea induced by ‘invasive’ bacteria	Racecadotril is a symptomatic treatment for acute diarrhoea. Medical advice should be sought if diarrhoea is associated with fever and/or bloody

	or purulent stools as this may indicate the presence of invasive bacteria or other serious diseases and if diarrhoea is associated with the use of antibiotics (pseudomembranous colitis).

PVI.Table 6 Missing information

Risk	What is known
Patients with renal (kidney) and hepatic (liver) insufficiency (poor function)	There are limited data for the use of racecadotril in patients with renal and hepatic impairment. These patients should be treated with caution. Special care is required and these patients should be treated only under medical supervision. Racecadotril is eliminated as both active and inactive metabolites. Elimination is mainly via the renal route.
Pregnant or breast-feeding women	Pregnancy: There are no adequate data from the use of racecadotril in pregnant women. Animal studies don't indicate direct or indirect harmful effects with respect to pregnancy, fertility, embryo or foetal development, parturition or postnatal development. Since no specific clinical studies are available, however, racecadotril should not be administered to pregnant women. Breast-feeding: There is insufficient information on the excretion of racecadotril in human milk; therefore racecadotril should not be administered to breastfeeding women.

Part VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have an SmPC, which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, and 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.

This medicine has no additional risk minimisation measures.

Part VI.2.6 Planned post-authorisation development plan

Not applicable.

Part VI.2.7 Summary of changes to the RMP over time

Not applicable

PART VI.3 ABBREVIATIONS

DLP	Data Lock Point
MAH	Marketing Authorisation Holder
PL	Package Leaflet
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

PART VI.4 REFERENCES

Part VI.4.1 Published references

Not applicable.

Part VI.4.2 Unpublished references

Not applicable.