EU Risk Management Plan for Palonosetron Seacross (Palonosetron hydrochloride)

RMP version to be assessed as part of this application:

RMP Version number:	0.1
Data lock point for this RMP:	22 July, 2019
Date of final sign-off:	29 Oct., 2019
QPPV name:	[redacted]
QPPV signature:	[redacted]

Table of content

Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Palonosetron hydrochloride
Pharmacotherapeutic group(s) (ATC Code)	Antiemetics and antinauseants, serotonin ($5HT_3$) antagonists (A04AA05).
Marketing Authorisation Holder	Seacross Pharmaceuticals Limited Seasec Pharmaceutical Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Palonosetron Seacross
Marketing authorisation procedure	National
Brief description of the product	Chemical class The chemical name of palonosetron hydrochloride is (3aS)-2-[(3S)-1-azabicyclo[2.2.2]oct-3-yl]- 2,3,3a,4,5,6-hexahydro-1H-benz[de]-isoquinolin-1-one hydrochloride corresponding to the molecular formula $C_{19}H_{24}N_2O$ HCl and has a relative molecular mass of 332.87 g/mol.
	Summary of mode of action Palonosetron is a 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors. Cancer chemotherapy may be associated with a high incidence of nausea and vomiting, particularly when certain agents, such as cisplatin, are used. 5-HT_3 receptors are located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone of the area postrema. It is thought that chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine and that the released serotonin then activates 5-HT_3 receptors located on vagal afferents to initiate the vomiting reflex. Postoperative nausea and vomiting is influenced by multiple patient, surgical and anesthesia related factors and is triggered by release of 5-HT in a cascade of neuronal events involving both the central nervous system and the gastrointestinal tract. The 5-HT_3 receptor has been demonstrated to selectively participate in the emetic response.
	Important information about its composition

	Not applicable.
Hyperlink to the Product Information	Please refer to eCTD sequence 0000 dossier section 1.3.1.
Indication(s) in the EEA	Current: Palonosetron Hydrochloride is indicated in adults for: • The prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy, • The prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy. Palonosetron Hydrochloride is indicated in paediatric patients 1 month of age and older for: • The prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.
	Proposed (if applicable): None.
Dosage in the EEA	Current: Palonosetron Hydrochloride should be used only before chemotherapy administration. This medicinal product should be administered by a healthcare professional under appropriate medical supervision. <u>Posology</u> *Adults* 250 micrograms palonosetron administered as a single intravenous bolus approximately 30 minutes before the start of chemotherapy. Palonosetron Hydrochloride should be injected over 30 seconds. The efficacy of Palonosetron Hydrochloride in the prevention of nausea and vomiting induced by highly emetogenic chemotherapy may be enhanced by the addition of a corticosteroid administered prior to chemotherapy. *Elderly people* No dose adjustment is necessary for the elderly. *Paediatric population* *Children and Adolescents (aged 1 month to 17 years):* 20 micrograms/kg (the maximum total dose should not exceed 1500 micrograms) palonosetron administered as a single 15 minute intravenous infusion beginning approximately 30 minutes before the start of chemotherapy. The safety and efficacy of Palonosetron Hydrochloride in children aged less than 1 month have not been

	established. No data are available. There are limited data on the use of Palonosetron Hydrochloride in the prevention of nausea and vomiting in children under 2 years of age. *Hepatic impairment* No dose adjustment is necessary for patients with impaired hepatic function. *Renal impairment* No dose adjustment is necessary for patients with impaired renal function. No data are available for patients with end stage renal disease undergoing haemodialysis.
	Proposed (if applicable): None.
Pharmaceutical form(s) and strengths	Current (if applicable): Solution for injection, 50mg/1ml
	Proposed (if applicable): None.
Is/will the product be subject to additional monitoring in the EU?	No.

Part II: Safety specification

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Severe constipation; • Severe hypersensitivity reactions.
Important potential risks	• QT/QTc prolongation; • Convulsive events; • Serotonin syndrome ; • Injection site reactions.
Missing information	• Effect in pregnancy; • Effect in lactating women; • Effects on fertility; • Effect in children aged less than 1 month (potential off-label use for CINV prevention); • Effects in patients with end stage renal disease undergoing haemodialysis.

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

No studies required.

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities conducted by the MAH include but not limited to:

- Regular safety data reconciliation with all relevant parties;
- Regularly performing scientific literature search and reports;
- Preparing and submitting periodic benefit-risk evaluation reports as per the requirement;
- Dealing with product complaints associated with AEs;
- Following up AE reports;
- Answering medical enquiries;
- Answering CA's requests on drug safety;
- PV SOPs regular review & upgrade;
- Article 57 Database maintenance;
- PSMF & SPS maintenance;
- Other general management of safety.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for safety concerns:

Not applicable.

Other forms of routine pharmacovigilance activities for safety concerns:

Not applicable.

III.2 Additional pharmacovigilance activities

Not applicable.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

Part VI: Summary of the risk management plan

Summary of risk management plan for Palonosetron Seacross (Palonosetron hydrochloride)

This is a summary of the risk management plan (RMP) for Palonosetron Seacross. The RMP details important risks of Palonosetron Seacross, and how more information will be obtained about Palonosetron Seacross's risks and uncertainties (missing information).

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

I. The medicine and what it is used for

Palonosetron Seacross is indicated in adults for:

- The prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy,
- The prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

Palonosetron Hydrochloride is indicated in paediatric patients 1 month of age and older for:

- The prevention of acute nausea and vomiting associated with highly emetogenic cancer chemotherapy and prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

See SmPC for the full indication. It contains palonosetron hydrochloride as the active substance and it is given by intravenous injection.

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

Important risks of Palonosetron Seacross, together with measures to minimise such risks and the proposed studies for learning more about Palonosetron Seacross'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 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 (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

II.A List of important risks and missing information

Important risks of Palonosetron Seacross are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Palonosetron Seacross. 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	• Severe constipation; • Severe hypersensitivity reactions.
Important potential risks	• QT/QTc prolongation; • Convulsive events; • Serotonin syndrome ; • Injection site reactions.
Missing information	• Effect in pregnancy; • Effect in lactating women; • Effects on fertility; • Effect in children aged less than 1 month (potential off-label use for CINV prevention); • Effects in patients with end stage renal disease undergoing haemodialysis.

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

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 Palonosetron Seacross.

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

There are no studies required for Palonosetron Seacross.

Part VII: Annexes

Table of contents

Annex 1 – EudraVigilance Interface

Not applicable.

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable.

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable.

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable. .

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Annex 7 - Other supporting data (including referenced material)

Not applicable.

Annex 8 – Summary of changes to the risk management plan over time

Version	**Approval date Procedure**	**Change**
0.1	N/A	Initial establishment.