VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Nausea and vomiting are common ailments had by many individuals. Nausea is defined as the unpleasant, painless sensation that one may potentially vomit. Vomiting involves the forceful expulsion of stomach contents through involuntary muscular contractions1. The causes of nausea and vomiting include food allergies, Infections of the stomach or bowels, such as the "stomach flu" or food poisoning, Leaking of stomach contents (food or liquid) upwards (also called gastroesophageal reflux or GERD), Medications or medical treatments, such as cancer chemotherapy or radiation treatments, Migraine headaches, Morning sickness during pregnancy, Seasickness or motion sickness and Severe pain, such as with kidney stones[2].

Nausea and vomiting do not pose an immediate threat to life, but the main concern is loss of water from the body (dehydration), which can lead to reduced nutrition in the body. Patients are often told to drink clear liquids to stay hydrated. Oral hydrating solutions are recommended for children."

VI.2.2 Summary of treatment benefits

Domperidone is used to relieve feelings of sickness (nausea) or being sick (vomiting). Feeling sick can be a common symptom, but it may be due to a number of different causes. Domperidone works by helping to move the food in the stomach through the digestive system more quickly. This helps to stop feeling sick.

VI.2.3 Unknowns relating to treatment benefits

Domperidone data in support of the paediatric use in relief of symptoms of nausea and vomiting is limited and it is not expected that the mechanism of action will differ between adults and children. However, further studies required to evaluate the efficacy of domperidone administration in children.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Cardiac events (QTc prolongation, serious ventriculararrhythmia,T orsade de Pointes, sudden cardiac deaths (SCD)) Heart events (electrocardiogram heart problem called 'prolonged QT corrected interval', irregular heartbeat, sudden heart death)	Domperidone has been associated with electrocardiogram heart problem called 'prolonged QT corrected interval', irregular heartbeat, sudden heart death	Patients with known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances (hypokalaemia- low blood potassium, hyperkalaemiaexcessive potassium in blood , hypomagnesaemia- low blood magnesium), or bradycardia (slow heart beat), or patients with underlying cardiac diseases such as congestive heart failure due to increased risk of ventricular arrhythmia should not use domperidone. It is recommended to monitor ECG.
Off-label use (e.g. stimulation of lactation in breast feeding women, gastroesophageal reflux disease, diabetic and non-diabetic gastroparesis, symptoms of postural hypotension in patients with Parkinson's disease)	No clinical trials have been performed to demonstrate safety and efficacy data of use of domperidone in stimulation of lactation in breastfeeding women, in treating chronic heart burn, diabetic and non-diabetic delayed gastric emptying, or symptoms of postural low blood pressure in patients with Parkinson's disease.	Domperidone should be administered only on prescription
Side effects relating to the nervous system in babies Neurological side effects in infants	The risk of side effects relating to the nervous system is higher in young children. Adverse reactions affecting the central nervous system are very rare in infants. These adverse reactions reverse spontaneously and completely as soon as the treatment is stopped. Other central nervous system-related effects of fits, agitation, and somnolence are also rare and	Domperidone should be administered only by prescription. These adverse reactions reverse spontaneously and completely as soon as the treatment is stopped.

Risk	What is known	Preventability
	primarily reported in infants. Overdose has been reported primarily in infants. Symptoms of overdosage may include agitation, altered consciousness, fits, confusion, somnolence and adverse reactions related to part of central nervous system. The risk of abnormal muscle movements is greatest in infants.	

Important potential risks

None

Missing information

Evaluation of the safe and effective use in paediatric patients to treat nausea and vomiting at the new recommended dosage (0.25mg/kg up to three times a day)	For children (less than 12 years of age) and adolescents weighing less than 35 kg, the tablets are out of place. If domperidone is for a child, the doctor should be asked for the children's formulation. Domperidone should be used at the lowest effective dose in children.

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

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

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimization measures).

These additional risk minimization measures are for the following risks:

Cardiac events (QTc prolongation, Torsade de Pointes, serious ventricular, arrhythmia, sudden cardiac deaths)

Risk minimisation measure(s) Dear Healthcare Professional Communication (DHPC)
Objective and rationale Dear Healthcare Professional Communication (DHPC) alerting all prescribing physicians on the potential of cardiac events. Inform prescribers and other healthcare professionals of the variation of the marketing authorisations for domperidone. Raise awareness of the new recommendations in the Product Information and risk minimisation measures.
Proposed action:

Updated SmPC and PIL, Insertion of black triangle (▼) in the SmPC and PIL indicating thatproduct is subject of additional monitoring. Furthermore, SmPC has been updated in relation with sections: 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, 5.2, 5.3. Sections 1, 2, 3, 4 of the PIL also be updated

Distribution of a DHPC

Summary description of the DHPC
The letter to health-care professionals to be provided to HPC includes advice on:
- Use of domperidone only in the relief of the symptoms of nausea and vomiting
- Treatment duration should not exceed 1 week
- The lowest effective dose should be used
- New recommended doses for adults, adolescents and children
- Contraindication in patients with severe hepatic impairment, conditions where the cardiac conduction intervals are impaired or could be affected and underlying cardiac diseases as congestive heart failure, when co-administered with QT-prolonging drugs or potent CYP3A4 inhibitors.

VI.2.6 Planned post authorisation development plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Planned date for submission of (interim and) final results
Drug Utilisation Study A Post-Authorisation Safety Study (PASS) to Assess the Effectiveness of the Risk Minimisation Measures of Domperidone – Physician Survey Category (1)	The primary objective of the study is to characterise prescribers' knowledge, understanding and extent of awareness regarding the new safety information for domperidone following the change in SmPC and the distribution of DHPC	Off-label use - e.g. stimulation of lactation in breast feeding women, gastroesophageal reflux disease, diabetic and non-diabetic gastroparesis, symptoms of postural hypotension in patients with Parkinson's disease	1. Protocol submission V 1.0	Submitted on 11 Feb 2015
			2. Protocol submission V 2.0	Submitted on 11 Jun 2015
			3. Updated protocol submission	10 March 2016
			3.DHPC distribution	AUG-DEC2014
			4. Start of data collection	4 months after approval of the protocol by Health Authorities
			5. End of data collection	4 months after start of data collection
			6.Study progress report	Not applicable

			7.Interim report	Not applicable
			8.Registration in the EU PAS register	Before the start of data collection
			9.Final report of study results	6 months after the end of data collection
A Drug Utilisation Study of Domperidone in Europe Using Databases Category (1)	The objective of the study is to investigate the effectiveness of risk minimisation measures and describe prescribing patterns of domperidone, including those pertaining to the off-label use of domperidone, in routine clinical practice in 3 European countries.		1. Protocol submission	Submitted on 11 Jun 2015
			2. Updated protocol submission	10 March 2016
			2. Start of data collection	Two months after protocol approval
			3End of data collection	When data through SEP2015 become available for analysis (estimated as 2Q2016)
			4.<Registration in the EU PAS Register>	Before the start of the study
			5. Final report of study results*	Twelve months after the end of data collection
*Timing of final report includes the following: Data analysis: three months after data are available Final tables available: Two months after data analysis is complete Report writing: Three months Report review (full Consortium): Four months				

PAES:.

No extra efficacy study is required for this product as it is not indicated for treating children under 12 years of age.

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
5.0	13 June 2016	-	Risk management plan v4.0 (Part VI) has been updated as suggested by assessor (DK).
4.0	28 March 2016	-	Risk management plan v3.0 (Part VI) has been updated as suggested by assessor. Updated protocols have been appended in Annex-6
3.0	12 June 2015	Safety concerns have been updated per assessor comment (MEB netherlands) Important identified risks : -Cardiac events (QTc prolongation; serious ventricular arrhythmia; Torsades de Pointes; sudden cardiac death (SCD)) -Off-label use (stimulation of lactation in breastfeeding women; gastro-oesophageal reflux disease; diabetic and non-diabetic gastroparesis; treatment of the symptoms of postural hypotension in patients with Parkinson's disease) use of the 30 mg suppositories in the paediatric population) -Neurological side effects in infants Important potential risks : None Missing information : -Evaluation of the safe and effective use in paediatric patients to treat nausea and vomiting at the new recommended dosage (0.25mg/kg up to three times a day)	RMP Version 3.0 has been updated with safety concernes proposed by assessor. Current DUS protocol has been appended in this version as Annex-6 The following MAHs details have been changed as per current MAs: Actavis A/S Sucursal to Aurovitas Unipessoal Lda and Actavis B.V. to Aurobindo Pharma B.V. Product name updation in NL: Domperidon Actavis 10 mg, omhulde tabletten to Domperidon Aurobindo 10 mg, omhulde tabletten Domperidone products are authorised under the legal basis of Article 10(1) of Directive 2001/83/EC, currently no routine PSURs need to submit hence annual safety reviews was considered as routine pharmacovigilance for safety concerns and same was amended relevant sections of the RMP V 3.0 .
2.0	14 October 2014	Safety concerns were updated in line with PRAC recommendations and current product information.	Version 1.0 is updated in line within GVP module to include the

		Important identified risks -Hypersensitivity to the active substance -Use in patients with prolactin-releasing pituitary tumour (prolactinoma) -Use in patients with renal impairment -Use in patients with hepatic impairment -Neurological side effects in children -Concomitant use with CYP3A4 inhibitors (oral ketoconazole, erythromycin or other potent CYP3A4 inhibitors) -Cardiac events (QTc prolongation, Torsade de Pointes, serious ventricular, arrhythmia, sudden cardiac deaths) -Off-label use (e.g. stimulation of lactation in breast feeding women, gastroesophageal reflux disease, diabetic and non-diabetic gastroparesis, symptoms of postural hypotension in patients with Parkinson's disease) -Co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects) -Co-administration with moderate CYP3A4 inhibitors(diltiazem, verapamil and some macrolides) -Co-administration with bradycardia and hypokalaemia inducing drugs Important potential risks -Use in pregnancy and lactation Missing information -Use in paediatric population	PRAC recommendations.