Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	minimization.	
Cerebrovascular accident	Currently available data do not support the need for risk minimization.	None
Pulmonary infections	Currently available data do not support the need for risk minimization.	None
Death	Currently available data do not support the need for risk minimization.	None

7.2 Part VI.2 Elements for a Public Summary

7.2.1 Part VI.2.1 Overview of disease epidemiology

Yearly occurrence of Alzheimer's dementia was estimated to be 7.5 per 1000 people with only difference across countries in Africa where numbers were lower. (Qiu et al. 2007) Annually approximately 53 people out of 1000 are diagnosed with Alzheimer's disease (AD) in the age of 65-74 in US increasing to 170 out of 1000 people aged 75-84 years and 231 out of 1000 people in the age of > 85 years. (Alzheimer's Association 2012). Others reported that age-specific incidence of AD showed no significant difference by gender (Mebane-Sims 2009). There are differences in yearly occurrence of AD in different countries: 60-65 years old: 2.5/1000 in Europe, 6.1/1000 in US and 0.7/1000 in Asia; 85-89 years old: numbers increased to 46.1/1000, 38.4/1000 and 39.7/1000, respectively (Kukull et al. 2000).

7.2.2 Part VI.2.2 Summary of treatment benefits

Rivastigmine, a treatment for mild to moderate Alzheimer disease (AD), is the first cholinesterase inhibitor to be available in the transdermal format. Most caregivers of patients with mild to moderate AD preferred the transdermal format of rivastigmine to the oral format. Caregivers also reported overall satisfaction, ease of use, and reduced impact on daily activities for transdermal rivastigmine format, in addition to patient improvement compared to their condition under the previous treatment (Reñé R et al.2013). The rivastigmine transdermal patch is effective in maintaining cognitive function over 18 months of treatment in patients with mild-to-moderate AD (Gauthier S et al 2013).

7.2.3 Part VI.2.3 Unknowns relating to treatment benefits

None

7.2.4 Part VI.2.4 Summary of safety concerns

Table 7-5 Important identified risks

Risk	What is known	Preventability
Gastrointestinal symptoms (nausea, vomiting, and diarrhea)	Gastrointestinal disorders such as nausea, vomiting and diarrhea may occur when initiating treatment and/or increasing the	Could be controlled with dose adjustment tailored to individual patient needs.

Risk	What is known	Preventability
	dose of rivastigmine. The patients may respond to a dose reduction. Prolonged vomiting or diarrhea can result in dehydration.	
Worsening of motor symptoms associated with Parkinson's disease	Dementia in the setting of Parkinson's disease usually sets in at a late stage of the disease. The clinical presentation of the disease is usually variable. Severe cortical cholinergic deficit accompanying the disease is considered to be correlated with the cognitive and behavioral dysfunction. Cholinergic stimulation in patients with PD may have the potential of exacerbating motor symptoms of the disease.	No definitive diagnostic tests exist to measure disease condition and stage disease. No apparent pattern for patient's feature to prevent/predict the adverse event. Motor symptoms of PD are identifiable clinically by neurological examination. The adverse reactions observed with rivastigmine are reversible when dose is decreased or the drug is discontinued.
Pancreatitis	Cholinergic stimulation may enhance secretion of pancreatic enzymes.	Currently unknown since no risk factors have been established.
Cardiac arrhythmias	As an important adverse event for all anticholinesterase inhibitors, cardiac arrhythmia is potentially significant for the target patient population who is elderly and may have pre-existing heart disorders and take co-medications that may potentially interact with rivastigmine leading to increased risk for cardiac arrhythmia. In severe cases, cardiac arrhythmia may lead to sudden death.	Caution should be exercised for patients with a history of cardiac arrhythmias or conduction abnormalities. Dose titration is recommended for patients who experienced this adverse event associated with the use of rivastigmine.
Exacerbations of asthma and COPD	Rivastigmine while promoting acetylcholine has the potential to increase bronchoconstriction and bronchial secretion with tendency to exacerbate preexisting chronic obstructive lung disease.	Caution should be exercised when treating patients with a history of asthma or COPD. Dose titration is recommended for patients who experienced this adverse event associated with the use of rivastigmine.
Application site skin reactions and irritations	Severity of skin reactions can range from a mild rash or pruritus to severe generalized skin reactions and in rare instances can lead to death.	No preventive measures known other than avoidance of exposure in patients with a known history of hypersensitivity to rivastigmine or its ingredients.
Hypertension	Cholinesterase inhibition may lead to alteration in blood pressure.	Identification of hypertension or risk factors for hypertension and proper management of preexisting hypertension or risk factors for developing hypertension may help prevent hypertension while receiving treatment with rivastigmine.
Gastrointestinal ulceration, hemorrhage, and perforation	Cholinergic stimulation has the potential to increase gastric acid	Avoidance of non-steroidal anti-inflammatory drugs while being

Risk	What is known	Preventability
	secretion that may lead to ulceration of the stomach and duodenum.	treated with rivastigmine. Patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those with an increased risk of developing ulcers such as those with a history of ulcer disease or patients using concurrent non-steroidal anti-inflammatory drugs.
Seizures	Cholinesterase inhibitors as a class have the potential to cause seizures.	Caution is advised when prescribing rivastigmine to patients who are at increased risk for seizures. Proper management of preexisting risk factors for seizures may help reduce the potential for developing seizures while receiving rivastigmine.
Hallucinations	Patients with AD or PDD are at increased risk for hallucinations. The risk is greater among patients with advanced disease than those with early stage of disease.	There are no reliable or valid tests available to predict patients who may be at increased risk for developing this adverse event.
Syncope and loss of consciousness	Syncope/loss of consciousness may be neurological or cardiac in origin and may result in falls associated with injuries (head trauma, fracture etc), which may lead to death in some cases.	Proper management of baseline risks for syncope such as cardiovascular diseases, prudent use of multiple drugs that may increase the effects of acetylcholinesterase inhibitors (AChEIs) and careful dose titration of AChEIs may lower the risk of developing syncope. In addition, prevention of dehydration and hypotension may also reduce the risk.
Medication misuse	Failure to strictly follow the instruction on how to use rivastigmine patch in the package insert contributes to this risk. Patients or care-givers who cannot understand and/or do not follow the instruction for use of rivastigmine patch increase the chances of misuse and experiencing adverse events associated with medication misuse.	To strictly follow the instruction for use of rivastigmine patches can prevent misuse and adverse events associated with medication misuse.
Medication errors	Failure to strictly follow the instruction on how to use rivastigmine patch in the package insert contributes to this risk. Patients or care-givers who cannot understand and/or do not follow	To strictly follow the instruction for use of rivastigmine patches can prevent adverse events associated with medication errors.

Risk	What is known	Preventability
	the instruction for use of rivastigmine patch increase the chances of experiencing adverse events associated with medication errors.	
Liver disorders	Patients with clinically significant hepatic impairment might experience more adverse reactions.	No dose adjustment is necessary for patients with mild to moderate hepatic impairment. However, due to increased exposure in this population dosing recommendations to titrate according to individual tolerability should be closely followed.
Severe skin reactions (bullous reactions)	Severity of skin reactions can range from a mild rash or pruritus to severe generalized skin reactions and in rare instances can lead to death.	No preventive measures known other than avoidance of exposure in patients with a known history of hypersensitivity to rivastigmine or its ingredients.

Table 7-6 Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Myocardial infarction	Drugs such as rivastigmine may have effects on heart rate (e.g., slow heart beat (bradycardia)). The potential for this action may be particularly important to patients with sick sinus or other supraventricular cardiac conduction conditions. Thus, it is mechanistically plausible that the event of myocardial infarction may be induced by rivastigmine treatment.
Cerebrovascular accident (Stroke)	No specific risk groups or risk factors have been established other than the risk factors common to cerebrovascular accident such as hypertension, hyperlipidemia, atrial fibrillation, diabetes etc.
Pulmonary infections	Rivastigmine while promoting acetylcholine has the potential to increase bronchoconstriction and bronchial secretion with tendency to exacerbate preexisting chronic obstructive lung disease. Aggravation of asthma or COPD may increase the chances of developing pulmonary infections.
Death	Relative to the mortality rate in untreated AD population reported in the literature, the mortality rate observed from the rivastigmine post-marketing experience is also lower. It is possible that underreporting may exist in the post-marketing setting.

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

All medicines have a SmPC which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, 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 special conditions and restrictions for its safe and effective use (additional risk minimisation measures). These additional risk minimization measures are for the following risks:

Table 7-7 Summary of risk minimization measures for Medication errors and medication misuse

Risk minimization measure(s)
Summary description of main additional risk minimisation measures: Medication errors and Medication misuse Objective and rationale: To educate patients and caregivers on proper use of the patch, provide daily reminders on proper patch use and, through other pharmacovigilance activities to follow the efficacy of the risk minimization activities in reducing the number of reports of multiple patch use. Proposed action: <u>Patient reminder card</u> The combined medication record and instructions for use is a tool to be distributed globally through the marketing and sales organizations in all CPOs to physicians and pharmacists who will then distribute to patients and caregivers. It is intended as a device whereby the daily application of the patch is recorded and acts as a daily reminder to the patient or caregiver. It also contains body diagrams which can be used for instruction of the patient, as well as clearly indicating application site of each patch.

7.2.6 Part VI.2.6 Planned post authorisation development plan

None

7.2.7 Part VI.2.7 Summary of changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
2.0	14.07.2014	Risk of “acute renal failure” was removed from the section “Important potential risks”. Risk of “dehydration” was removed from section “Important identified risks”.	*Changes have been made according to the Pharmacovigilance Risk Assessment Committee report 05-Sep-2013/EMA/PRAC 473053/2013.* *The RMP was updated based on the Exelon®RMP version no. 8, dated 01 Apr 2014*
2.1	24 Feb 2015	N/A	The word "important" was removed from the wording important missing information according to the RMS Day 120 Assessment Report.