VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Alzheimer´s disease is the most common form of dementia. Advancing age is a primary risk factor for the disease. Most often, it is diagnosed in people over 65 years of age. The number of afflicted people worldwide is estimated to be around 25 million (2010 data) with 4 million new cases per year.

VI.2.2 Summary of treatment benefits

Efficacy of rivastigmine was evaluated in three studies which compared the safety and efficacy of different dose ranges (1-12 mg/day orally) of rivastigmine compared to placebo in patients with mild-to-moderate Alzheimer's disease. 1449 patients were randomised to receive rivastigmine treatment and 647 patients received placebo. Improvements in cognition (which include problems with memory, language, thinking and judgment that are greater than normal age-related changes), activities of daily living and overall response were measured as primary endpoints of the studies. Analysis of the results showed that patients receiving doses of 6 to 12 mg/day rivastigmine show statistically significant improvement in the measured endpoints in comparison to placebo.

9.5 mg/24 h transdermal patches show similar exposure to rivastigmine as when taking 12 mg/day of oral rivastigmine. The efficacy of 13.3 mg/24 h transdermal patch was demonstrated in a 48-week active comparator study which included 527 patients with Alzheimer's disease which were receiving either 13.3 mg/24 h or 9.5 mg/24 h of transdermal rivastigmine.

If administered as indicated in the Summary of Product Characteristics and taking into account the contra-indications, warnings and precautions, Rivastigmine 4.6 mg/24 h transdermal patch, Rivastigmine 9.5 mg/24 h transdermal patch and Rivastigmine 13.3 mg/24 h transdermal patch can be considered effective in the approved indications and generally well tolerated.

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

Risk	What is known	Preventability
Symptoms of the stomach and the bowel (Nausea, vomiting and diarrhoea) (Gastrointestinal symptoms [Nausea, vomiting and diarrhoea])	Nausea, vomiting and diarrhoea have been observed in 1/100 up to less than 1/10 patients. Occurrence of nausea, vomiting and diarrhoea is dependent on the dose, may occur when initiating treatment and/or when increasing the dose and is more frequent in women.	Patient should inform his/her doctor of pharmacist if he/she has a gastrointestinal reaction such as feeling sick (nausea), being sick (vomiting) and diarrhoea. The doctor may need to monitor the patient more closely while he/she is on this medicine. Treatment should be interrupted in case of nausea, vomiting and diarrhoea until these adverse reactions resolve.
Worsening of symptoms associated with Parkinson's (Worsening of motor symptoms associated with Parkinson's disease)	Worsening of Parkinson's disease, such as tremor, slowness of movement, rigidity, impaired balance, extrapyramidal side effects (inability to initiate movement, inability to remain motionless, muscular spasms), has been observed; frequency is not known. Extrapyramidal side effects may be exacerbated or induced. Extrapyramidal symptoms have been observed in less than 1/10,000 patients	Patient should inform his/her doctor of pharmacist if he/she suffers from trembling. The doctor may need to monitor the patient more closely while he/she are on this medicine.
Inflammation of the pancreas (Pancreatitis)	Inflammation of the pancreas has been observed; frequency is not known	None.

Risk	What is known	Preventability
Irregular heart beat (Cardiac arrhythmias)	Reduced heart beat has been observed in 1/1,000 up to less than 1/100 patients.	Patient should inform his/her doctor of pharmacist if he/she has or ever had an irregular heartbeat. The doctor may need to monitor the patient more closely while he/she is on this medicine. Care must be taken in patients with abnormal heart rhythm (sick-sinus syndrome or conduction defects [sino-atrial block, atrio-ventricular block])
Impairment of asthma and of lung disease (Exacerbation of asthma and COPD)	Impairment of asthma and of lung disease, which is characterised by cough, shortage of breath and secretion may occur	Patient should inform his/her doctor of pharmacist if he/she has or ever had asthma or a severe respiratory disease. The doctor may need to monitor the patient more closely while he/she is on this medicine. Care must be taken in patients with a history of asthma or obstructive pulmonary disease.
Local reaction at the application site of the patch (Application site skin reactions and irritations with patch use)	Local reaction at the application site of the patch (reddening, pruritus, oedema, irritation, dermatitis) has been observed in 1/100 up to less than 1/10 patients. Local reactions at the application site of the patch are mild or moderate in intensity. Skin application site reactions are not themselves an indication of sensitisation, but rivastigmine patch may lead to allergic contact dermatitis; allergic contact dermatitis should be suspected if application site reactions spread beyond the patch size. Patients sensitised to rivastigmine by exposure to the patch may not be able to take rivastigmine in any form.	The transdermal patch should not be applied to skin that is red, irritated or cut. Do not apply a new patch to that same skin area twice within 14 days. If there is evidence of a more intense local reaction or if symptoms do not significantly improve within 48 h after patch removal; then treatment should be discontinued. Patients suggestive of allergic contact dermatitis to rivastigmine patch who still require rivastigmine should be only switched to oral rivastigmine after negative allergy testing and under close supervision by a physician.
Increase in blood pressure (Hypertension)	Increase in blood pressure may occur	None.

Risk	What is known	Preventability
Ulcer of the stomach or bowel, bleeding, and perforation (Gastrointestinal ulceration, haemorrhage, and perforation)	Ulcer of the stomach has been observed in 1/1,000 up to less than 1/100 patients. Ulcer of the bowels and bleeding have been observed in less than 1/10,000 patients with capsules and oral solution, and not with patches	Patient should inform his/her doctor of pharmacist if he/she has or ever had an active stomach ulcer. The doctor may need to monitor the patient more closely while he/she is on this medicine. Care must be taken in patients with active ulcers of the stomach or duodenum, or patients predisposed to these conditions because rivastigmine may cause increased secretions of the stomach.
Rapid and uncontrollable body shakes (Seizures)	Rapid and uncontrollable body shakes have been observed; frequency not known.	Patient should inform his/her doctor of pharmacist if he/she has or ever had seizures. The doctor may need to monitor the patient more closely while he/she is on this medicine. Care must be taken in patients predisposed to rapid and uncontrollable body shakes because drugs that mimic the action of acetylcholine may induce or exacerbate this disease.
Hallucinations	Hallucination has been observed with frequency not known. Symptoms of overdose can include hallucinations.	None.
Loss of consciousness (Syncope and loss of consciousness)	Loss of consciousness has been observed in 1/100 up to less than 1/10 patients.	None.

Risk	What is known	Preventability
- Misuse of the patch (Medication misuse) - Administrations errors (Medication errors with patch use)	Misuse and dosing errors have resulted in serious adverse reactions; some cases have required hospitalisations and led to death in rare cases. Overdose (due to administration error) has been observed. Symptoms of overdose include nausea, vomiting and diarrhoea, increase in blood pressure or hallucinations, and changes in heart rate. In cases of overdose without symptoms all transdermal rivastigmine patches should be removed immediately and no further transdermal patch should be applied for the next 24 hours. In overdose with severe nausea and vomiting, the use of drugs which inhibit nausea and vomiting should be considered. Treatment of symptoms for other adverse reactions should be given as necessary. In massive overdose, atropine can be used. An initial dose of 0.03 mg/kg intravenous atropine sulphate is recommended, with subsequent doses based on clinical response. Use of scopolamine as an antidote is not recommended.	Patients and caregivers should be instructed on important administration instructions - removal of the previous day's patch before applying a new one every day; patch should be replaced by a new one after 24 hours; only one patch should be worn at a time; the patch should be pressed down firmly for at least 30 seconds using the palm of the hand until the edges stick well; if the patch falls off, a new one should be applied for the rest of the day, then it should be replaced at the same time as usual the next day; the patch can be used in everyday situations, including bathing and during hot weather; the patch should not be exposed to any external heat sources for long periods of time; the patch should not be cut into pieces.
Liver disorders	Inflammation of the liver and elevated liver function tests have been observed; frequency is unknown. Dose must not be reduced in patients with liver disorders. Patients with severe liver disorders might have more adverse reactions.	Patient should inform his/her doctor of pharmacist if he/she has impaired liver function. The doctor may need to monitor the patient more closely while he/she is on this medicine. In patients with significantly impaired liver function the doctor may consider using the 4.6 mg/24 h transdermal patch as initial and maximum dose.
Severe skin reactions (skin lesions characterised by large reddening with blisters) (Severe skin reactions [bullous reactions])	Allergic reaction of the skin affecting the whole body has been observed irrespective of route of administration (oral, transdermal). Disseminated cutaneous hypersensitivity reactions have been observed.	Patients should not use rivastigmine patches if they are allergic to rivastigmine, similar type of medicine (carbamate derivatives) or any of the other ingredients of this medicine. Treatment should be discontinued in case of occurrence.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Heart attack (Myocardial infarction)	When higher doses than 9.5 mg/24 h were used, heart failure has been observed more frequently than with 9.5 mg/24 h or placebo; heart failure seems to be dependent on the dose. Heart pain has been observed with capsules and oral solution, but not with the patch. As heart failure has been observed with the patch and heart pain has been observed with the capsule or solution, heart attack may occur.
Stroke (Cerebrovascular accidents)	Stroke (rapid loss of brain function due to disturbance in the blood supply to the brain) may occur. (Reason not known)
Infection of the lungs (Pulmonary infections)	Infection of the lungs may occur. (Reason not known)
Death	Misuse of the medicinal product and dosing errors have resulted in serious adverse reactions; some cases have required hospitalisation, and rarely led to death.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (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.

Rivastigmine 4.6 mg/24 h and 9.5 mg/24 h transdermal patches have no additional risk minimisation measures.

Rivastigmine 13.3 mg/24 h transdermal patch has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Implementation in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risks:

Misuse of the patch and administrations errors

Risk minimisation measure(s) **Educational material (for 13.3mg/24 h dose only)should contain the following elements:** • **SmPC** • **patient diary (patient reminder card)** • **instructions to provide patients and caregivers with the patient diary (patient reminder card)**
Objective and rationale
To reduce the risk of overdoses due to incorrect application of 13.3mg/24 h rivastigmine patch and to increase the risk-benefit ratio of the product
Proposed action

Risk minimisation measure(s) **Educational material (for 13.3mg/24 h dose only)should contain the following elements:** • **SmPC** • **patient diary (patient reminder card)** • **instructions to provide patients and caregivers with the patient diary (patient reminder card)**
The patient diary (patient reminder card) should contain the following key messages: • Take off the previous patch before putting ONE new patch on. • Only one patch per day. • Do not cut the patch into pieces. • Press the patch firmly in place for at least 30 seconds using the palm of the hand. • How to use the patient diary (patient reminder card) to record patch application and removal.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Table 2. Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	23 July 2012	Identified Risks - Worsening of symptoms associated with Parkinson's disease; Nausea, vomiting and diarrhoea; Increased amylase, lipase and pancreatitis; Application site reactions and irritations; Anaemia; Eye irritation; Pulmonary infections; Cardiac arrhythmias; Exacerbation of asthma and COPD; Cardiac disorders (myocardial infarction); Liver disorders (hepatitis); Haematuria; Cerebrovascular accidents; Urinary tract obstruction; Gastric ulcer; Death; Bullous reactions; Seizures; Delirium; Pyrexia; Aggression; Overdose (due to administration error). Potential Risks - none Missing information - none	Safety concerns for rivastigmine 4.6 mg/24 h and 9.5 mg/24 h transdermal patch that have been identified and listed in v 1.0 were based on the EPAR for the brand leader from 2007 (Exelon, Novartis).
2.0	25 March 2013	Identified risks added: Hallucinations, Syncope and loss of consciousness, Medication misuse with patch, Dehydration. Identified risks renamed: Nausea, vomiting and diarrhoea to Gastrointestinal symptoms, Increased amylase, lipase and pancreatitis to Pancreatitis, Gastric ulcer to Gastrointestinal ulceration, haemorrhage, and perforation, Overdose (due to administration error) to Medication errors with patch. Anaemia, Eye irritation, Haematuria, Urinary tract obstruction, Delirium,	All safety concerns for Teva's generic products have been updated in accordance with the current Exelon RMP. Removed safety concerns are not listed as important identified risks in the current Exelon RMP. Terms Anaemia, Haematuria, Urinary tract obstruction do not fall within definition of identified risks, i.e. risks are not stated in the labelling.

Version	Date	Safety Concerns	Comment
		Parexia, Aggression removed as identified risks. Acute renal failure added as a potential risk. Pulmonary infections, myocardial infarction, Cerebrovascular accidents and Death moved to potential risks.	RMP has been updated based on Guidance on format of the risk management plan (RMP) in the EU for Generics
2.1	14 June 2013	Unchanged	Amendment of section VI.2.1 ("Overview of disease epidemiology").
2.2	16 December 2013	Unchanged	Rivastigmine 13.3mg/24 h transdermal patch included in the RMP.
2.3	24 September 2014	Not applicable	Not applicable - preapproval version(s)