ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine 3M Health Care Ltd. 4.6 mg/24 h transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each transdermal patch releases 4.6 mg of rivastigmine per 24 hours. Each transdermal patch of 4.15 cm^2 contains 7.17 mg of rivastigmine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patch

Rectangular patches, approximately 2.5 cm by 1.8 cm with rounded corners. Each patch consists of a combination of a removable, transparent, split release liner, a functional layer containing drug-in-adhesive (DIA) matrix, and a protective backing layer. The backing layer is transparent to translucent, labelled with "R5" in a repeated pattern.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of mild to moderately severe Alzheimer's dementia.

4.2 Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's dementia. Diagnosis should be made according to current guidelines. Similar to any treatment initiated in patients with dementia, therapy with rivastigmine should only be started if a caregiver is available to regularly administer and monitor the treatment.

Posology

Transdermal patches	**Rivastigmine *in vivo* release rates per 24 h**
Rivastigmine 4.6 mg/24 h	4.6 mg
Rivastigmine 9.5 mg/24 h	9.5 mg
Rivastigmine 13.3 mg/24 h*	13.3 mg

*A marketing authorisation for Rivastigmine 3M Health Care Ltd. 13.3 mg/24 h transdermal patch is currently not available, this presentation may although be available from other marketing authorisation holders.

Initial dose
Treatment is started with 4.6 mg/24 h.

Maintenance dose
After a minimum of four weeks of treatment and if well tolerated according to the treating physician, the dose of 4.6 mg/24 h should be increased to 9.5 mg/24 h, the daily recommended effective dose, which should be continued for as long as the patient continues to demonstrate therapeutic benefit.

Dose escalation
9.5 mg/24 h is the recommended daily effective dose which should be continued for as long as the patient continues to demonstrate therapeutic benefit. If well tolerated and only after a minimum of six months of treatment at 9.5 mg/24 h, the treating physician may consider increasing the dose to 13.3 mg/24 h in patients who have demonstrated a meaningful cognitive deterioration (e.g. decrease in the MMSE) and/or functional decline (based on physician judgement) while on the recommended daily effective dose of 9.5 mg/24 h (see section 5.1).

The clinical benefit of rivastigmine should be reassessed on a regular basis. Discontinuation should also be considered when evidence of a therapeutic effect at the optimal dose is no longer present.

Treatment should be temporarily interrupted if gastrointestinal adverse reactions are observed until these adverse reactions resolve. Transdermal patch treatment can be resumed at the same dose if treatment is not interrupted for more than three days. Otherwise treatment should be re-initiated with 4.6 mg/24 h.

Switching from capsules or oral solution to transdermal patches
Based on comparable exposure between oral and transdermal rivastigmine (see section 5.2), patients treated with rivastigmine capsules or oral solution can be switched to Rivastigmine 3M Health Care Ltd. transdermal patches as follows:
- A patient on a dose of 3 mg/day oral rivastigmine can be switched to 4.6 mg/24 h transdermal patches.
- A patient on a dose of 6 mg/day oral rivastigmine can be switched to 4.6 mg/24 h transdermal patches.
- A patient on a stable and well tolerated dose of 9 mg/day oral rivastigmine can be switched to 9.5 mg/24 h transdermal patches. If the oral dose of 9 mg/day has not been stable and well tolerated, a switch to 4.6 mg/24 h transdermal patches is recommended.
- A patient on a dose of 12 mg/day oral rivastigmine can be switched to 9.5 mg/24 h transdermal patches.

After switching to 4.6 mg/24 h transdermal patches, provided these are well tolerated after a minimum of four weeks of treatment, the dose of 4.6 mg/24 h should be increased to 9.5 mg/24 h, which is the recommended effective dose.

It is recommended to apply the first transdermal patch on the day following the last oral dose.

Special populations
- Paediatric population: There is no relevant use of Rivastigmine 3M Health Care Ltd. in the paediatric population in the treatment of Alzheimer's disease.
- Patients with body weight below 50 kg: Particular caution should be exercised in titrating patients with body weight below 50 kg above the recommended effective dose of 9.5 mg/24 h (see section 4.4). They may experience more adverse reactions and may be more likely to discontinue due to adverse reactions.
- Hepatic impairment: No dose adjustment is necessary for patients with hepatic impairment. However, due to increased exposure in these populations as observed with the oral forms, dosing recommendations to titrate according to individual tolerability should be closely followed as patients with clinically significant hepatic impairment might experience more adverse reactions. Patients with severe hepatic impairment have not been studied (see sections 4.4 and 5.2).
- Renal impairment: No dose adjustment is necessary for patients with renal impairment. However, due to increased exposure in these populations as observed with the oral forms, dosing recommendations to titrate according to individual tolerability should be closely followed as patients with clinically significant renal impairment might experience more adverse reactions (see sections 4.4 and 5.2).

Method of administration
Transdermal patches should be applied once a day to clean, dry, hairless, intact healthy skin on the upper or lower back, upper arm or chest, in a place which will not be rubbed by tight clothing. It is not

recommended to apply the transdermal patch to the thigh or to the abdomen due to decreased bioavailability of rivastigmine observed when the transdermal patch is applied to these areas of the body.

The transdermal patch should not be applied to skin that is red, irritated or cut. Reapplication to the exact same skin location within 14 days should be avoided to minimise the potential risk of skin irritation.

Patients and caregivers should be instructed on important administration instructions:
- The previous day's patch must be removed before applying a new one every day (see section 4.9).
- The patch should be replaced by a new one after 24 hours. Only one patch should be worn at a time (see section 4.9).
- 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 (e.g. excessive sunlight, saunas, solarium) for long periods of time.
- The patch should not be cut into pieces.

4.3 Contraindications

The use of this medicinal product is contraindicated in patients with known hypersensitivity to the active substance rivastigmine, to other carbamate derivatives or to any of the excipients listed in section 6.1.

Previous history of application site reactions suggestive of allergic contact dermatitis with rivastigmine patch (see section 4.4).

4.4 Special warnings and precautions for use

The incidence and severity of adverse reactions generally increase with increasing doses, particularly at dose changes. If treatment is interrupted for more than three days, it should be re-initiated with 4.6 mg/24 h.

Misuse of the medicinal product and dosing errors resulting in overdose
Misuse of the medicinal product and dosing errors with rivastigmine transdermal patches have resulted in serious adverse reactions; some cases have required hospitalisation, and rarely led to death (see section 4.9). Most cases of misuse of the medicinal product and dosing errors have involved not removing the old patch when putting on a new one and the use of multiple patches at the same time. Patients and their caregivers must be instructed on important administration instructions for Rivastigmine 3M Health Care Ltd. transdermal patch (see section 4.2).

Gastrointestinal disorders
Gastrointestinal disorders such as nausea, vomiting and diarrhoea are dose-related, and may occur when initiating treatment and/or increasing the dose (see section 4.8). These adverse reactions occur more commonly in women. Patients who show signs or symptoms of dehydration resulting from prolonged vomiting or diarrhoea can be managed with intravenous fluids and dose reduction or discontinuation if recognised and treated promptly. Dehydration can be associated with serious outcomes.

Weight loss
Patients with Alzheimer's disease may lose weight whilst taking cholinesterase inhibitors, including rivastigmine. The patient's weight should be monitored during therapy with Rivastigmine 3M Health Care Ltd. transdermal patches.

Other adverse reactions
Care must be taken when prescribing Rivastigmine 3M Health Care Ltd. transdermal patches:
- to patients with sick sinus syndrome or conduction defects (sino-atrial block, atrio-ventricular

block) (see section 4.8)
- to patients with active gastric or duodenal ulcers or patients predisposed to these conditions because rivastigmine may cause increased gastric secretions (see section 4.8)
- to patients predisposed to urinary obstruction and seizures because cholinomimetics may induce or exacerbate these diseases.
- to patients with a history of asthma or obstructive pulmonary disease.

Skin application site reactions
Skin application site reactions may occur with rivastigmine patch and are usually mild or moderate in intensity. Patients and caregivers should be instructed accordingly.

These reactions are not in themselves an indication of sensitisation. However, use of rivastigmine patch may lead to allergic contact dermatitis.

Allergic contact dermatitis should be suspected if application site reactions spread beyond the patch size, if there is evidence of a more intense local reaction (e.g. increasing erythema, oedema, papules, vesicles) and if symptoms do not significantly improve within 48 hours after patch removal. In these cases, treatment should be discontinued (see section 4.3).

Patients who develop application site reactions suggestive of allergic contact dermatitis to rivastigmine patch and who still require rivastigmine treatment should only be switched to oral rivastigmine after negative allergy testing and under close medical supervision. It is possible that some patients sensitised to rivastigmine by exposure to rivastigmine patch may not be able to take rivastigmine in any form.

There have been rare post-marketing reports of patients experiencing disseminated skin hypersensitivity reactions when administered rivastigmine irrespective of the route of administration (oral, transdermal). In these cases, treatment should be discontinued (see section 4.3).

Other warnings and precautions

Rivastigmine may exacerbate or induce extrapyramidal symptoms.

Contact with the eyes should be avoided after handling Rivastigmine 3M Health Care Ltd. transdermal patches (see section 5.3). Hands should be washed with soap and water after removing the patch. In case of contact with eyes or if the eyes become red after handling the patch, rinse immediately with plenty of water and seek medical advice if symptoms do not resolve.

Special populations:
- Patients with body weight below 50 kg may experience more adverse reactions and may be more likely to discontinue due to adverse reactions (see section 4.2). Carefully titrate and monitor these patients for adverse reactions (e.g. excessive nausea or vomiting) and consider reducing the maintenance dose to the 4.6 mg/24 h transdermal patch if such adverse reactions develop.
- Hepatic impairment: Patients with clinically significant hepatic impairment might experience more adverse reactions (see sections 4.2 and 5.2). Consider using the 4.6 mg/24 h transdermal patch both as initial and **maximum** dose in these patients.
- Renal impairment: Patients with clinically significant renal impairment might experience more adverse reactions (see sections 4.2 and 5.2). Consider using the 4.6 mg/24 h transdermal patch both as initial and maximum dose in these patients.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed with Rivastigmine 3M Health Care Ltd. transdermal patches.

As a cholinesterase inhibitor, rivastigmine may exaggerate the effects of succinylcholine-type muscle

relaxants during anaesthesia. Caution is recommended when selecting anaesthetic agents. Possible dose adjustments or temporarily stopping treatment can be considered if needed.

In view of its pharmacodynamic effects, rivastigmine should not be given concomitantly with other cholinomimetic substances and might interfere with the activity of anticholinergic medicinal products.

No pharmacokinetic interaction was observed between oral rivastigmine and digoxin, warfarin, diazepam or fluoxetine in studies in healthy volunteers. The increase in prothrombin time induced by warfarin is not affected by administration of oral rivastigmine. No untoward effects on cardiac conduction were observed following concomitant administration of digoxin and oral rivastigmine.

Concomitant administration of rivastigmine with commonly prescribed medicinal products, such as antacids, antiemetics, antidiabetics, centrally acting antihypertensives, beta blockers, calcium channel blockers, inotropic agents, antianginals, non-steroidal anti-inflammatory agents, oestrogens, analgesics, benzodiazepines and antihistamines, was not associated with an alteration in the kinetics of rivastigmine or an increased risk of clinically relevant untoward effects.

According to its metabolism, metabolic interactions with other medicinal products appear unlikely, although rivastigmine may inhibit the butyrylcholinesterase mediated metabolism of other substances.

4.6 Fertility, pregnancy and lactation

Pregnancy
No clinical data on exposed pregnancies are available. In peri/postnatal studies in rats, an increased gestation time was observed. Rivastigmine should not be used during pregnancy unless clearly necessary.

Breast-feeding
In animals, rivastigmine is excreted into milk. It is not known if rivastigmine is excreted into human milk. Therefore, women on rivastigmine should not breast-feed.

Fertility
No effects on fertility or embryofoetal development were observed in rats and rabbits, except at doses related to maternal toxicity.

4.7 Effects on ability to drive and use machines

Alzheimer's disease may cause gradual impairment of driving performance or compromise the ability to use machines. Furthermore, rivastigmine may induce syncope or delirium. As a consequence, rivastigmine has minor or moderate influence on the ability to drive and use machines. Therefore, in patients with dementia treated with rivastigmine, the ability to continue driving or operating complex machines should be routinely evaluated by the treating physician.

4.8 Undesirable effects

Summary of the safety profile
Application site skin reactions (usually mild to moderate application site erythema), are the most frequent adverse reactions observed with the use of rivastigmine transdermal patch. The next most common adverse reactions are gastrointestinal in nature including nausea and vomiting.

Adverse reactions in Table 1 are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Tabulated list of adverse reactions

Table 1 displays the adverse reactions reported in 854 patients with Alzheimer's dementia treated in randomised, double-blind, placebo and active-controlled clinical studies with rivastigmine transdermal patches for a duration of 24-48 weeks and from post-marketing data.

Table 1

Infections and infestations	
Common	Urinary tract infection
Metabolism and nutrition disorders	
Common	Anorexia, decreased appetite
Uncommon	Dehydration
Psychiatric disorders	
Common	Anxiety, depression, delirium, agitation
Uncommon	Aggression
Not known	Hallucinations, restlessness
Nervous system disorders	
Common	Headache, syncope, dizziness
Uncommon	Psychomotor hyperactivity
Very rare	Extrapyramidal symptoms
Not known	Worsening of Parkinson's disease, seizure
Cardiac disorders	
Uncommon	Bradycardia
Not known	Atrioventricular block, atrial fibrillation, tachycardia, sick sinus syndrome
Vascular disorders	
Not known	Hypertension
Gastrointestinal disorders	
Common	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain
Uncommon	Gastric ulcer
Not known	Pancreatitis
Hepatobiliary disorders	
Not known	Hepatitis, elevated liver function tests
Skin and subcutaneous tissue disorders	
Common	Rash
Not known	Pruritus, erythema, urticaria, vesicles, allergic dermatitis, disseminated cutaneous hypersensitivity reactions
Renal and urinary disorders	
Common	Urinary incontinence
General disorders and administration site conditions	
Common	Application site skin reactions (e.g. application site erythema, application site pruritus, application site oedema, application site dermatitis, application site irritation), asthenic conditions (e.g. fatigue, asthenia), pyrexia, weight decreased
Rare	Fall

Description of selected adverse reactions

When doses higher than 13.3 mg/24 h were used in the above-mentioned placebo-controlled study, insomnia and cardiac failure were observed more frequently than with 13.3 mg/24 h or placebo, suggesting a dose effect relationship. However, these events did not occur at a higher frequency with rivastigmine 13.3 mg/24 h transdermal patches than with placebo.

The following adverse reactions have only been observed with rivastigmine capsules and oral solution and not in clinical studies with rivastigmine transdermal patches: somnolence, malaise, tremor, confusion, sweating increased (common); duodenal ulcers, angina pectoris (rare); gastrointestinal haemorrhage (very rare); and some cases of severe vomiting were associated with oesophageal rupture (not known).

Skin irritation
In a 24-week double-blind, placebo-controlled clinical trial, skin reactions were measured at each visit using a skin irritation rating scale that rated the degree of erythema, oedema, scaling, fissures, pruritus and pain/stinging/burning at the application site. The most commonly observed symptom was erythema which disappeared within 24 hours in the vast majority of patients. In the 24-week double-blind study, the most commonly observed symptoms (skin irritation rating scale) with rivastigmine 9.5 mg/24 h transdermal patches were very slight (21.8%), mild (12.5%) or moderate (6.5%) erythema or very slight (11.9%), mild (7.3%) or moderate (5.0%) pruritus. The most commonly observed severe symptoms with rivastigmine 9.5 mg/24 h transdermal patches were pruritus (1.7%) and erythema (1.1%). Most skin reactions were limited to the application site and resulted in discontinuation in only 2.4% of the patients in the rivastigmine 9.5 mg/24 h transdermal patch group.

In a 48-week active-controlled clinical trial, cases of skin irritation were captured as patient or caregiver reported adverse reactions. The most commonly reported skin irritation events during the first 24 weeks of the double-blind period with rivastigmine 13.3 mg/24 h transdermal patches and rivastigmine 9.5 mg/24 h transdermal patches, respectively were application site erythema (5.7% vs 4.6%) and application site pruritus (3.6% vs 2.8%). The percentages decreased in both rivastigmine 13.3 mg/24 h transdermal patch and rivastigmine 9.5 mg/24 h transdermal patch treatment groups over time (>24 weeks): application site erythema (0.8% vs. 1.6%) and application site pruritus (0.4% vs. 1.2%), respectively. Application site pruritus led to discontinuation in 1.1% of the patients from each of the treatment groups during the total 48-week double-blind treatment phase. Application site reactions were mostly mild to moderate in severity and were rated as severe in less than 2% of patients.

A direct comparison of the rate of skin irritation events reported in each of these studies cannot be made due to the difference in data collection methods employed.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Most cases of accidental overdose of oral rivastigmine have not been associated with any clinical signs or symptoms and almost all of the patients concerned continued rivastigmine treatment. Where symptoms have occurred, they have included nausea, vomiting and diarrhoea, hypertension or hallucinations. Due to the known vagotonic effect of cholinesterase inhibitors on heart rate, bradycardia and/or syncope may also occur. Ingestion of 46 mg of oral rivastigmine occurred in one case; following conservative management the patient fully recovered within 24 hours. Overdose with rivastigmine transdermal patches resulting from misuse/dosing errors (application of multiple patches at a time) has been reported in the post-marketing setting. The typical symptoms reported among these cases are similar to those seen with cases of overdose associated with rivastigmine oral formulations.

Treatment
As rivastigmine has a plasma half-life of about 3.4 hours and a duration of acetylcholinesterase inhibition of about 9 hours, it is recommended that in cases of asymptomatic overdose all Rivastigmine 3M Health Care Ltd. transdermal patches should be removed immediately and no further transdermal patch should be applied for the next 24 hours. In overdose accompanied by severe nausea and vomiting, the use of antiemetics should be considered. Symptomatic treatment 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psychoanaleptics, anticholinesterases, ATC code: N06DA03

Rivastigmine is an acetyl- and butyrylcholinesterase inhibitor of the carbamate type, thought to facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by functionally intact cholinergic neurones. Thus, rivastigmine may have an ameliorative effect on cholinergic-mediated cognitive deficits in dementia associated with Alzheimer's disease.

Rivastigmine interacts with its target enzymes by forming a covalently bound complex that temporarily inactivates the enzymes. In healthy young men, an oral 3 mg dose decreases acetylcholinesterase (AChE) activity in CSF by approximately 40% within the first 1.5 hours after administration. Activity of the enzyme returns to baseline levels about 9 hours after the maximum inhibitory effect has been achieved. In patients with Alzheimer's disease, inhibition of AChE in CSF by oral rivastigmine was dose-dependent up to 6 mg given twice daily, the highest dose tested. Inhibition of butyrylcholinesterase activity in CSF of 14 Alzheimer patients treated by oral rivastigmine was similar to the inhibition of AChE activity.

Clinical studies in Alzheimer's dementia

The efficacy of rivastigmine transdermal patches in patients with Alzheimer's dementia has been demonstrated in a 24-week double-blind, placebo-controlled core study and its open-label extension phase and in a 48-week double-blind comparator study.

24-week placebo-controlled study

Patients involved in the placebo-controlled study had an MMSE (Mini-Mental State Examination) score of 10–20. Efficacy was established by the use of independent, domain-specific assessment tools which were applied at regular intervals during the 24-week treatment period. These include the ADAS-Cog (Alzheimer's Disease Assessment Scale – Cognitive subscale, a performance-based measure of cognition) and the ADCS-CGIC (Alzheimer's Disease Cooperative Study – Clinician's Global Impression of Change, a comprehensive global assessment of the patient by the physician incorporating caregiver input), and the ADCS-ADL (Alzheimer's Disease Cooperative Study – Activities of Daily Living, a caregiver-rated assessment of the activities of daily living including personal hygiene, feeding, dressing, household chores such as shopping, retention of ability to orient oneself to surroundings as well as involvement in activities related to finances). The 24-week results for the three assessment tools are summarised in Table 2.

Table 2

ITT-LOCF population	**Rivastigmine transdermal patches 9.5 mg/24 h N = 251**	**Rivastigmine capsules 12 mg/day N = 256**	**Placebo N = 282**
ADAS-Cog			
	(n=248)	(n=253)	(n=281)
Mean baseline ± SD	27.0 ± 10.3	27.9 ± 9.4	28.6 ± 9.9
Mean change at week 24 ± SD	-0.6 ± 6.4	-0.6 ± 6.2	1.0 ± 6.8
p-value versus placebo	0.005*[1]	0.003*[1]	
ADCS-CGIC			
	(n=248)	(n=253)	(n=278)
Mean score ± SD	3.9 ± 1.20	3.9 ± 1.25	4.2 ± 1.26
p-value versus placebo	0.010*[2]	0.009*[2]	
ADCS-ADL			

	(n=247)	(n=254)	(n=281)
Mean baseline ± SD	50.1 ± 16.3	49.3 ± 15.8	49.2 ± 16.0
Mean change at week 24 ± SD	-0.1 ± 9.1	-0.5 ± 9.5	-2.3 ± 9.4
p-value versus placebo	0.013*[1]	0.039*[1]	

* p≤0.05 versus placebo
ITT: Intent-To-Treat; LOCF: Last Observation Carried Forward
[1] Based on ANCOVA with treatment and country as factors and baseline value as a covariate. Negative ADAS-Cog changes indicate improvement. Positive ADCS-ADL changes indicate improvement.
[2] Based on CMH test (van Elteren test) blocking for country. ADCS-CGIC scores <4 indicate improvement.

The results for clinically relevant responders from the 24-week placebo-controlled study are provided in Table 3. Clinically relevant improvement was defined a priori as at least 4-point improvement on the ADAS-Cog, no worsening on the ADCS-CGIC, and no worsening on the ADCS-ADL.

Table 3

	Patients with clinically significant response (%)		
ITT-LOCF population	**Rivastigmine transdermal patches 9.5 mg/24 h N = 251**	**Rivastigmine capsules 12 mg/day N = 256**	**Placebo N = 282**
At least 4 points improvement on ADAS-Cog with no worsening on ADCS-CGIC and ADCS-ADL	17.4	19.0	10.5
p-value versus placebo	0.037*	0.004*	

*p<0.05 versus placebo

As suggested by compartmental modelling, 9.5 mg/24 h transdermal patches exhibited exposure similar to that provided by an oral dose of 12 mg/day.

48-week active comparator controlled study
Patients involved in the active comparator controlled study had an initial baseline MMSE score of 10-24. The study was designed to compare the efficacy of the 13.3 mg/24 h transdermal patch against the 9.5 mg/24 h transdermal patch during a 48-week double-blind treatment phase in Alzheimer's disease patients who demonstrated functional and cognitive decline after an initial 24-48 week open-label treatment phase while on a maintenance dose of 9.5 mg/24 h transdermal patch. Functional decline was assessed by the investigator and cognitive decline was defined as a decrease in the MMSE score of ≥4 points from the previous visit or a decrease of ≥3 points from baseline. Efficacy was established by the use of ADAS-Cog (Alzheimer's Disease Assessment Scale – Cognitive subscale, a performance-based measure of cognition) and the ADCS-IADL (Alzheimer's Disease Cooperative Study – Instrumental Activities of Daily Living) assessing instrumental activities which include maintaining finances, meal preparation, shopping, ability to orient oneself to surroundings, ability to be left unattended. The 48-week results for the two assessment tools are summarised in Table 4.

Table 4

Population/Visit		**Rivastigmine 13.3 mg/24 h N = 265**		**Rivastigmine 9.5 mg/24 h N = 271**		**Rivastigmine 13.3 mg/24 h**		**Rivastigmine 9.5 mg/24 h**
		n	**Mean**	**n**	**Mean**	**DLSM**	**95% CI**	**p-value**
ADAS-Cog								
LOCF	Baseline	264	34.4	268	34.9			

	DB-week 48	Value	264	38.5	268	39.7			
		Change	264	4.1	268	4.9	-0.8	(-2.1, 0.5)	0.227
ADCS-IADL									
LOCF		Baseline	265	27.5	271	25.8			
	Week 48	Value	265	23.1	271	19.6			
		Change	265	-4.4	271	-6.2	2.2	(0.8, 3.6)	0.002*

CI – confidence interval.
DLSM – difference in least square means.
LOCF – Last Observation Carried Forward.
ADAS-cog scores: A negative difference in DLSM indicates greater improvement in Rivastigmine 13.3 mg/24 h as compared to Rivastigmine 9.5 mg/24 h.
ADCS-IADL scores: A positive difference in DLSM indicates greater improvement in Rivastigmine 13.3 mg/24 h as compared to Rivastigmine 9.5 mg/24 h.
N is the number of patients with an assessment at baseline (last assessment in the initial open-label phase) and with at least 1 post-baseline assessment (for the LOCF).
The DLSM, 95% CI, and p-value are based on an ANCOVA (analysis of covariance) model adjusted for country and baseline ADAS-cog score.
* $p<0.05$

The European Medicines Agency has waived the obligation to submit the results of studies with rivastigmine in all subsets of the paediatric population in the treatment of Alzheimer's dementia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Absorption of rivastigmine from rivastigmine transdermal patches is slow. After the first dose, detectable plasma concentrations are observed after a lag time of 0.5-1 hour. C_{max} is reached after 10-16 hours. After the peak, plasma concentrations slowly decrease over the remainder of the 24-hour period of application. With multiple dosing (such as at steady state), after the previous transdermal patch is replaced with a new one, plasma concentrations initially decrease slowly for about 40 minutes on average, until absorption from the newly applied transdermal patch becomes faster than elimination, and plasma levels begin to rise again to reach a new peak at approximately 8 hours. At steady state, trough levels are approximately 50% of peak levels, in contrast to oral administration, with which concentrations fall off to virtually zero between doses. Although less pronounced than with the oral formulation, exposure to rivastigmine (C_{max} and AUC) increased over-proportionally by a factor of 2.6 and 4.9 when escalating from 4.6 mg/24 h to 9.5 mg/24 h and to 13.3 mg/24 h, respectively. The fluctuation index (FI), a measure of the relative difference between peak and trough concentrations ($(C_{max}-C_{min})/C_{avg}$), was 0.58 for rivastigmine 4.6 mg/24 h transdermal patches, 0.77 for rivastigmine 9.5 mg/24 h transdermal patches and 0.72 for rivastigmine 13.3 mg/24 h transdermal patches, thus demonstrating a much smaller fluctuation between trough and peak concentrations than for the oral formulation (FI = 3.96 (6 mg/day) and 4.15 (12 mg/day)).

The dose of rivastigmine released from the transdermal patch over 24 hours (mg/24 h) cannot be directly equated to the amount (mg) of rivastigmine contained in a capsule with respect to plasma concentration produced over 24 hours.

The single-dose inter-subject variability in rivastigmine pharmacokinetic parameters (normalised to dose/kg bodyweight) was 43% (C_{max}) and 49% (AUC_{0-24h}) after transdermal administration versus 74% and 103%, respectively, after the oral form. The inter-patient variability in a steady-state study in Alzheimer's dementia was at most 45% (C_{max}) and 43% (AUC_{0-24h}) after use of the transdermal patch, and 71% and 73%, respectively, after administration of the oral form.

A relationship between active substance exposure at steady state (rivastigmine and metabolite

NAP226-90) and bodyweight was observed in Alzheimer's dementia patients. Compared to a patient with a body weight of 65 kg, the rivastigmine steady-state concentrations in a patient with a body weight of 35 kg would be approximately doubled, while for a patient with a body weight of 100 kg the concentrations would be approximately halved. The effect of bodyweight on active substance exposure suggests special attention to patients with very low body weight during up-titration (see section 4.4).

Exposure (AUC_∞) to rivastigmine (and metabolite NAP266-90) was highest when the transdermal patch was applied to the upper back, chest, or upper arm and approximately 20–30% lower when applied to the abdomen or thigh.

There was no relevant accumulation of rivastigmine or the metabolite NAP226-90 in plasma in patients with Alzheimer's disease, except that plasma levels were higher on the second day of transdermal patch therapy than on the first.

Distribution
Rivastigmine is weakly bound to plasma proteins (approximately 40%). It readily crosses the blood-brain barrier and has an apparent volume of distribution in the range of 1.8-2.7 l/kg.

Biotransformation
Rivastigmine is rapidly and extensively metabolised with an apparent elimination half-life in plasma of approximately 3.4 hours after removal of the transdermal patch. Elimination was absorption rate limited (flip-flop kinetics), which explains the longer $t_{½}$ after transdermal patch (3.4 h) versus oral or intravenous administrations (1.4 to 1.7 h). Metabolism is primarily via cholinesterase-mediated hydrolysis to the metabolite NAP226-90. *In vitro*, this metabolite shows minimal inhibition of acetylcholinesterase (<10%). Based on evidence from *in vitro* and animal studies, the major cytochrome P450 isoenzymes are minimally involved in rivastigmine metabolism. Total plasma clearance of rivastigmine was approximately 130 litres/h after a 0.2 mg intravenous dose and decreased to 70 litres/h after a 2.7 mg intravenous dose, which is consistent with the non-linear, over-proportional pharmacokinetics of rivastigmine due to saturation of its elimination.

The metabolite-to-parent AUC_∞ ratio was around 0.7 after transdermal patch administration versus 3.5 after oral administration, indicating that much less metabolism occurred after dermal compared to oral treatment. Less NAP226-90 is formed following application of the transdermal patch, presumably because of the lack of presystemic (hepatic first pass) metabolism, in contrast to oral administration.

Elimination
Unchanged rivastigmine is found in trace amounts in the urine; renal excretion of the metabolites is the major route of elimination after transdermal patch administration. Following administration of oral ^{14}C-rivastigmine, renal elimination was rapid and essentially complete (>90%) within 24 hours. Less than 1% of the administered dose is excreted in the faeces.

Elderly population
Age had no impact on the exposure to rivastigmine in Alzheimer's disease patients treated with rivastigmine transdermal patches.

Hepatic impairment
No study was conducted with rivastigmine transdermal patches in subjects with hepatic impairment. After oral administration, the C_{max} of rivastigmine was approximately 60% higher and the AUC of rivastigmine was more than twice as high in subjects with mild to moderate hepatic impairment than in healthy subjects.

Renal impairment
No study was conducted with rivastigmine transdermal patches in subjects with renal impairment. After oral administration, C_{max} and AUC of rivastigmine were more than twice as high in Alzheimer patients with moderate renal impairment compared with healthy subjects; however there were no changes in C_{max} and AUC of rivastigmine in Alzheimer patients with severe renal impairment.

5.3 Preclinical safety data

Oral and topical repeated-dose toxicity studies in mice, rats, rabbits, dogs and minipigs revealed only effects associated with an exaggerated pharmacological action. No target organ toxicity was observed. Oral and topical dosing in animal studies was limited due to the sensitivity of the animal models used.

Rivastigmine was not mutagenic in a standard battery of *in vitro* and *in vivo* tests, except in a chromosomal aberration test in human peripheral lymphocytes at a dose exceeding 10^4 times the foreseen clinical exposure. The *in vivo* micronucleus test was negative.

No evidence of carcinogenicity was found in oral and topical studies in mice and in an oral study in rats at the maximum tolerated dose. The exposure to rivastigmine and its metabolites was approximately equivalent to human exposure with highest doses of rivastigmine capsules and transdermal patches.

In animals, rivastigmine crosses the placenta and is excreted into milk. Oral studies in pregnant rats and rabbits gave no indication of teratogenic potential on the part of rivastigmine. Specific dermal studies in pregnant animals have not been conducted.

Rivastigmine transdermal patches were not phototoxic. In some other dermal toxicity studies, a mild irritant effect on the skin of laboratory animals, including controls, was observed. This may indicate a potential for rivastigmine transdermal patches to induce mild erythema in patients. When administered to rabbit eyes in primary eye irritation studies, rivastigmine caused reddening and swelling of the conjunctiva, corneal opacities and miosis which persisted for 7 days. Therefore, the patient/caregiver should avoid contact with the eyes after handling of the patch (see section 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Backing layer
Polyester and ethyl vinyl acetate

Drug-in-adhesive (DIA) matrix
Acrylate copolymer adhesive
Isopropyl myristate

Release liner
Polyester

6.2 Incompatibilities

To prevent interference with the adhesive properties of the transdermal patch, no cream, lotion or powder should be applied to the skin area where the medicinal product is to be applied.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Heat-sealed pouches made of paper/aluminium/acrylonitrile-methacrylate copolymer laminate. One pouch contains one transdermal patch.

Available in packs containing 7, 30, 60 and 90 pouches.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Used transdermal patches should be folded in half, with the adhesive side inwards, placed in the original pouch and discarded safely and out of the sight and reach of children.
Any used or unused transdermal patches should be disposed of in accordance with local requirements or returned to the pharmacy.

7. MARKETING AUTHORISATION HOLDER

3M Health Care Limited,
1 Morley Street,
Loughborough,
Leicestershire,
LE11 1EP
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/14/911/001
EU/1/14/911/002
EU/1/14/911/003
EU/1/14/911/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine 3M Health Care Ltd. 9.5 mg/24 h transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each transdermal patch releases 9.5 mg of rivastigmine per 24 hours. Each transdermal patch of 8.3 cm^2 contains 14.33 mg of rivastigmine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patch

Rectangular patches, approximately 3.5 cm by 2.6 cm with rounded corners. Each patch consists of a combination of a removable, transparent, split release liner, a functional layer containing drug-in-adhesive (DIA) matrix, and a protective backing layer. The backing layer is transparent to translucent, labelled with "R10" in a repeated pattern.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of mild to moderately severe Alzheimer's dementia.

4.2 Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's dementia. Diagnosis should be made according to current guidelines. Similar to any treatment initiated in patients with dementia, therapy with rivastigmine should only be started if a caregiver is available to regularly administer and monitor the treatment.

Posology

Transdermal patches	**Rivastigmine *in vivo* release rates per 24 h**
Rivastigmine 4.6 mg/24 h	4.6 mg
Rivastigmine 9.5 mg/24 h	9.5 mg
Rivastigmine 13.3 mg/24 h*	13.3 mg

*A marketing authorisation for Rivastigmine 3M Health Care Ltd. 13.3 mg/24 h transdermal patch is currently not available, this presentation may although be available from other marketing authorisation holders.

Initial dose
Treatment is started with 4.6 mg/24 h.

Maintenance dose
After a minimum of four weeks of treatment and if well tolerated according to the treating physician, the dose of 4.6 mg/24 h should be increased to 9.5 mg/24 h, the daily recommended effective dose, which should be continued for as long as the patient continues to demonstrate therapeutic benefit.

Dose escalation
9.5 mg/24 h is the recommended daily effective dose which should be continued for as long as the patient continues to demonstrate therapeutic benefit. If well tolerated and only after a minimum of six months of treatment at 9.5 mg/24 h, the treating physician may consider increasing the dose to 13.3 mg/24 h in patients who have demonstrated a meaningful cognitive deterioration (e.g. decrease in the MMSE) and/or functional decline (based on physician judgement) while on the recommended daily effective dose of 9.5 mg/24 h (see section 5.1).

The clinical benefit of rivastigmine should be reassessed on a regular basis. Discontinuation should also be considered when evidence of a therapeutic effect at the optimal dose is no longer present.

Treatment should be temporarily interrupted if gastrointestinal adverse reactions are observed until these adverse reactions resolve. Transdermal patch treatment can be resumed at the same dose if treatment is not interrupted for more than three days. Otherwise treatment should be re-initiated with 4.6 mg/24 h.

Switching from capsules or oral solution to transdermal patches
Based on comparable exposure between oral and transdermal rivastigmine (see section 5.2), patients treated with rivastigmine capsules or oral solution can be switched to Rivastigmine 3M Health Care Ltd. transdermal patches as follows:
- A patient on a dose of 3 mg/day oral rivastigmine can be switched to 4.6 mg/24 h transdermal patches.
- A patient on a dose of 6 mg/day oral rivastigmine can be switched to 4.6 mg/24 h transdermal patches.
- A patient on a stable and well tolerated dose of 9 mg/day oral rivastigmine can be switched to 9.5 mg/24 h transdermal patches. If the oral dose of 9 mg/day has not been stable and well tolerated, a switch to 4.6 mg/24 h transdermal patches is recommended.
- A patient on a dose of 12 mg/day oral rivastigmine can be switched to 9.5 mg/24 h transdermal patches.

After switching to 4.6 mg/24 h transdermal patches, provided these are well tolerated after a minimum of four weeks of treatment, the dose of 4.6 mg/24 h should be increased to 9.5 mg/24 h, which is the recommended effective dose.

It is recommended to apply the first transdermal patch on the day following the last oral dose.

Special populations
- Paediatric population: There is no relevant use of Rivastigmine 3M Health Care Ltd. in the paediatric population in the treatment of Alzheimer's disease.
- Patients with body weight below 50 kg: Particular caution should be exercised in titrating patients with body weight below 50 kg above the recommended effective dose of 9.5 mg/24 h (see section 4.4). They may experience more adverse reactions and may be more likely to discontinue due to adverse reactions.
- Hepatic impairment: No dose adjustment is necessary for patients with hepatic impairment. However, due to increased exposure in these populations as observed with the oral forms, dosing recommendations to titrate according to individual tolerability should be closely followed as patients with clinically significant hepatic impairment might experience more adverse reactions. Patients with severe hepatic impairment have not been studied (see sections 4.4 and 5.2).
- Renal impairment: No dose adjustment is necessary for patients with renal impairment. However, due to increased exposure in these populations as observed with the oral forms, dosing recommendations to titrate according to individual tolerability should be closely followed as patients with clinically significant renal impairment might experience more adverse reactions (see sections 4.4 and 5.2).

Method of administration
Transdermal patches should be applied once a day to clean, dry, hairless, intact healthy skin on the upper

or lower back, upper arm or chest, in a place which will not be rubbed by tight clothing. It is not recommended to apply the transdermal patch to the thigh or to the abdomen due to decreased bioavailability of rivastigmine observed when the transdermal patch is applied to these areas of the body.

The transdermal patch should not be applied to skin that is red, irritated or cut. Reapplication to the exact same skin location within 14 days should be avoided to minimise the potential risk of skin irritation.

Patients and caregivers should be instructed on important administration instructions:
- The previous day's patch must be removed before applying a new one every day (see section 4.9).
- The patch should be replaced by a new one after 24 hours. Only one patch should be worn at a time (see section 4.9).
- 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 (e.g. excessive sunlight, saunas, solarium) for long periods of time.
- The patch should not be cut into pieces.

4.3 Contraindications

The use of this medicinal product is contraindicated in patients with known hypersensitivity to the active substance rivastigmine, to other carbamate derivatives or to any of the excipients listed in section 6.1.

Previous history of application site reactions suggestive of allergic contact dermatitis with rivastigmine patch (see section 4.4).

4.4 Special warnings and precautions for use

The incidence and severity of adverse reactions generally increase with increasing doses, particularly at dose changes. If treatment is interrupted for more than three days, it should be re-initiated with 4.6 mg/24 h.

Misuse of the medicinal product and dosing errors resulting in overdose
Misuse of the medicinal product and dosing errors with rivastigmine transdermal patches have resulted in serious adverse reactions, some cases have required hospitalisation, and rarely led to death (see section 4.9). Most cases of misuse of the medicinal product and dosing errors have involved not removing the old patch when putting on a new one and the use of multiple patches at the same time. Patients and their caregivers must be instructed on important administration instructions for Rivastigmine 3M Health Care Ltd. transdermal patch (see section 4.2).

Gastrointestinal disorders
Gastrointestinal disorders such as nausea, vomiting and diarrhoea are dose-related, and may occur when initiating treatment and/or increasing the dose (see section 4.8). These adverse reactions occur more commonly in women. Patients who show signs or symptoms of dehydration resulting from prolonged vomiting or diarrhoea can be managed with intravenous fluids and dose reduction or discontinuation if recognised and treated promptly. Dehydration can be associated with serious outcomes.

Weight loss
Patients with Alzheimer's disease may lose weight whilst taking cholinesterase inhibitors, including rivastigmine. The patient's weight should be monitored during therapy with Rivastigmine 3M Health Care Ltd. transdermal patches.

Other adverse reactions
Care must be taken when prescribing Rivastigmine 3M Health Care Ltd. transdermal patches:

- to patients with sick sinus syndrome or conduction defects (sino-atrial block, atrio-ventricular block) (see section 4.8)
- to patients with active gastric or duodenal ulcers or patients predisposed to these conditions because rivastigmine may cause increased gastric secretions (see section 4.8)
- to patients predisposed to urinary obstruction and seizures because cholinomimetics may induce or exacerbate these diseases.
- to patients with a history of asthma or obstructive pulmonary disease.

Skin application site reactions
Skin application site reactions may occur with rivastigmine patch and are usually mild or moderate in intensity. Patients and caregivers should be instructed accordingly.

These reactions are not in themselves an indication of sensitisation. However, use of rivastigmine patch may lead to allergic contact dermatitis.

Allergic contact dermatitis should be suspected if application site reactions spread beyond the patch size, if there is evidence of a more intense local reaction (e.g. increasing erythema, oedema, papules, vesicles) and if symptoms do not significantly improve within 48 hours after patch removal. In these cases, treatment should be discontinued (see section 4.3).

Patients who develop application site reactions suggestive of allergic contact dermatitis to rivastigmine patch and who still require rivastigmine treatment should only be switched to oral rivastigmine after negative allergy testing and under close medical supervision. It is possible that some patients sensitised to rivastigmine by exposure to rivastigmine patch may not be able to take rivastigmine in any form.

There have been rare post-marketing reports of patients experiencing disseminated skin hypersensitivity reactions when administered rivastigmine irrespective of the route of administration (oral, transdermal). In these cases, treatment should be discontinued (see section 4.3).

Other warnings and precautions

Rivastigmine may exacerbate or induce extrapyramidal symptoms.

Contact with the eyes should be avoided after handling Rivastigmine 3M Health Care Ltd. transdermal patches (see section 5.3). Hands should be washed with soap and water after removing the patch. In case of contact with eyes or if the eyes become red after handling the patch, rinse immediately with plenty of water and seek medical advice if symptoms do not resolve.

Special populations:
- Patients with body weight below 50 kg may experience more adverse reactions and may be more likely to discontinue due to adverse reactions (see section 4.2). Carefully titrate and monitor these patients for adverse reactions (e.g. excessive nausea or vomiting) and consider reducing the maintenance dose to the 4.6 mg/24 h transdermal patch if such adverse reactions develop.
- Hepatic impairment: Patients with clinically significant hepatic impairment might experience more adverse reactions (see sections 4.2 and 5.2). Consider using the 4.6 mg/24 h transdermal patch both as initial and **maximum** dose in these patients.
- Renal impairment: Patients with clinically significant renal impairment might experience more adverse reactions (see sections 4.2 and 5.2). Consider using the 4.6 mg/24 h transdermal patch both as initial and maximum dose in these patients.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed with Rivastigmine 3M Health Care Ltd. transdermal patches.

As a cholinesterase inhibitor, rivastigmine may exaggerate the effects of succinylcholine-type muscle

relaxants during anaesthesia. Caution is recommended when selecting anaesthetic agents. Possible dose adjustments or temporarily stopping treatment can be considered if needed.

In view of its pharmacodynamic effects, rivastigmine should not be given concomitantly with other cholinomimetic substances and might interfere with the activity of anticholinergic medicinal products.

No pharmacokinetic interaction was observed between oral rivastigmine and digoxin, warfarin, diazepam or fluoxetine in studies in healthy volunteers. The increase in prothrombin time induced by warfarin is not affected by administration of oral rivastigmine. No untoward effects on cardiac conduction were observed following concomitant administration of digoxin and oral rivastigmine.

Concomitant administration of rivastigmine with commonly prescribed medicinal products, such as antacids, antiemetics, antidiabetics, centrally acting antihypertensives, beta blockers, calcium channel blockers, inotropic agents, antianginals, non-steroidal anti-inflammatory agents, oestrogens, analgesics, benzodiazepines and antihistamines, was not associated with an alteration in the kinetics of rivastigmine or an increased risk of clinically relevant untoward effects.

According to its metabolism, metabolic interactions with other medicinal products appear unlikely, although rivastigmine may inhibit the butyrylcholinesterase mediated metabolism of other substances.

4.6 Fertility, pregnancy and lactation

Pregnancy
No clinical data on exposed pregnancies are available. In peri/postnatal studies in rats, an increased gestation time was observed. Rivastigmine should not be used during pregnancy unless clearly necessary.

Breast-feeding
In animals, rivastigmine is excreted into milk. It is not known if rivastigmine is excreted into human milk. Therefore, women on rivastigmine should not breast-feed.

Fertility
No effects on fertility or embryofoetal development were observed in rats and rabbits, except at doses related to maternal toxicity.

4.7 Effects on ability to drive and use machines

Alzheimer's disease may cause gradual impairment of driving performance or compromise the ability to use machines. Furthermore, rivastigmine may induce syncope or delirium. As a consequence, rivastigmine has minor or moderate influence on the ability to drive and use machines. Therefore, in patients with dementia treated with rivastigmine, the ability to continue driving or operating complex machines should be routinely evaluated by the treating physician.

4.8 Undesirable effects

Summary of the safety profile
Application site skin reactions (usually mild to moderate application site erythema), are the most frequent adverse reactions observed with the use of rivastigmine transdermal patch. The next most common adverse reactions are gastrointestinal in nature including nausea and vomiting.

Adverse reactions in Table 1 are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Tabulated list of adverse reactions

Table 1 displays the adverse reactions reported in 854 patients with Alzheimer's dementia treated in randomised, double-blind, placebo and active-controlled clinical studies with rivastigmine transdermal patches for a duration of 24-48 weeks and from post-marketing data.

Table 1

Infections and infestations	
Common	Urinary tract infection
Metabolism and nutrition disorders	
Common	Anorexia, decreased appetite
Uncommon	Dehydration
Psychiatric disorders	
Common	Anxiety, depression, delirium, agitation
Uncommon	Aggression
Not known	Hallucinations, restlessness
Nervous system disorders	
Common	Headache, syncope, dizziness
Uncommon	Psychomotor hyperactivity
Very rare	Extrapyramidal symptoms
Not known	Worsening of Parkinson's disease, seizure
Cardiac disorders	
Uncommon	Bradycardia
Not known	Atrioventricular block, atrial fibrillation, tachycardia, sick sinus syndrome
Vascular disorders	
Not known	Hypertension
Gastrointestinal disorders	
Common	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain
Uncommon	Gastric ulcer
Not known	Pancreatitis
Hepatobiliary disorders	
Not known	Hepatitis, elevated liver function tests
Skin and subcutaneous tissue disorders	
Common	Rash
Not known	Pruritus, erythema, urticaria, vesicles, allergic dermatitis, disseminated cutaneous hypersensitivity reactions
Renal and urinary disorders	
Common	Urinary incontinence
General disorders and administration site conditions	
Common	Application site skin reactions (e.g. application site erythema, application site pruritus, application site oedema, application site dermatitis, application site irritation), asthenic conditions (e.g. fatigue, asthenia), pyrexia, weight decreased
Rare	Fall

Description of selected adverse reactions

When doses higher than 13.3 mg/24 h were used in the above-mentioned placebo-controlled study, insomnia and cardiac failure were observed more frequently than with 13.3 mg/24 h or placebo, suggesting a dose effect relationship. However, these events did not occur at a higher frequency with rivastigmine 13.3 mg/24 h transdermal patches than with placebo.

The following adverse reactions have only been observed with rivastigmine capsules and oral solution and not in clinical studies with rivastigmine transdermal patches: somnolence, malaise, tremor, confusion, sweating increased (common); duodenal ulcers, angina pectoris (rare); gastrointestinal haemorrhage (very rare); and some cases of severe vomiting were associated with oesophageal rupture (not known).

Skin irritation
In a 24-week double-blind, placebo-controlled clinical trial, skin reactions were measured at each visit using a skin irritation rating scale that rated the degree of erythema, oedema, scaling, fissures, pruritus and pain/stinging/burning at the application site. The most commonly observed symptom was erythema which disappeared within 24 hours in the vast majority of patients. In the 24-week double-blind study, the most commonly observed symptoms (skin irritation rating scale) with rivastigmine 9.5 mg/24 h transdermal patches were very slight (21.8%), mild (12.5%) or moderate (6.5%) erythema or very slight (11.9%), mild (7.3%) or moderate (5.0%) pruritus. The most commonly observed severe symptoms with rivastigmine 9.5 mg/24 h transdermal patches were pruritus (1.7%) and erythema (1.1%). Most skin reactions were limited to the application site and resulted in discontinuation in only 2.4% of the patients in the rivastigmine 9.5 mg/24 h transdermal patch group.

In a 48-week active-controlled clinical trial, cases of skin irritation were captured as patient or caregiver reported adverse reactions. The most commonly reported skin irritation events during the first 24 weeks of the double-blind period with rivastigmine 13.3 mg/24 h transdermal patches and rivastigmine 9.5 mg/24 h transdermal patches, respectively were application site erythema (5.7% vs 4.6%) and application site pruritus (3.6% vs 2.8%). The percentages decreased in both rivastigmine 13.3 mg/24 h transdermal patch and rivastigmine 9.5 mg/24 h transdermal patch treatment groups over time (>24 weeks): application site erythema (0.8% vs. 1.6%) and application site pruritus (0.4% vs. 1.2%), respectively. Application site pruritus led to discontinuation in 1.1% of the patients from each of the treatment groups during the total 48-week double-blind treatment phase. Application site reactions were mostly mild to moderate in severity and were rated as severe in less than 2% of patients.

A direct comparison of the rate of skin irritation events reported in each of these studies cannot be made due to the difference in data collection methods employed.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Most cases of accidental overdose of oral rivastigmine have not been associated with any clinical signs or symptoms and almost all of the patients concerned continued rivastigmine treatment. Where symptoms have occurred, they have included nausea, vomiting and diarrhoea, hypertension or hallucinations. Due to the known vagotonic effect of cholinesterase inhibitors on heart rate, bradycardia and/or syncope may also occur. Ingestion of 46 mg of oral rivastigmine occurred in one case; following conservative management the patient fully recovered within 24 hours. Overdose with rivastigmine transdermal patches resulting from misuse/dosing errors (application of multiple patches at a time) has been reported in the post-marketing setting. The typical symptoms reported among these cases are similar to those seen with cases of overdose associated with rivastigmine oral formulations.

Treatment
As rivastigmine has a plasma half-life of about 3.4 hours and a duration of acetylcholinesterase inhibition of about 9 hours, it is recommended that in cases of asymptomatic overdose all Rivastigmine 3M Health Care Ltd. transdermal patches should be removed immediately and no further transdermal patch should be applied for the next 24 hours. In overdose accompanied by severe nausea and vomiting, the use of antiemetics should be considered. Symptomatic treatment 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psychoanaleptics, anticholinesterases, ATC code: N06DA03

Rivastigmine is an acetyl- and butyrylcholinesterase inhibitor of the carbamate type, thought to facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by functionally intact cholinergic neurones. Thus, rivastigmine may have an ameliorative effect on cholinergic-mediated cognitive deficits in dementia associated with Alzheimer's disease.

Rivastigmine interacts with its target enzymes by forming a covalently bound complex that temporarily inactivates the enzymes. In healthy young men, an oral 3 mg dose decreases acetylcholinesterase (AChE) activity in CSF by approximately 40% within the first 1.5 hours after administration. Activity of the enzyme returns to baseline levels about 9 hours after the maximum inhibitory effect has been achieved. In patients with Alzheimer's disease, inhibition of AChE in CSF by oral rivastigmine was dose-dependent up to 6 mg given twice daily, the highest dose tested. Inhibition of butyrylcholinesterase activity in CSF of 14 Alzheimer patients treated by oral rivastigmine was similar to the inhibition of AChE activity.

Clinical studies in Alzheimer's dementia

The efficacy of rivastigmine transdermal patches in patients with Alzheimer's dementia has been demonstrated in a 24-week double-blind, placebo-controlled core study and its open-label extension phase and in a 48-week double-blind comparator study.

24-week placebo-controlled study

Patients involved in the placebo-controlled study had an MMSE (Mini-Mental State Examination) score of 10–20. Efficacy was established by the use of independent, domain-specific assessment tools which were applied at regular intervals during the 24-week treatment period. These include the ADAS-Cog (Alzheimer's Disease Assessment Scale – Cognitive subscale, a performance-based measure of cognition) and the ADCS-CGIC (Alzheimer's Disease Cooperative Study – Clinician's Global Impression of Change, a comprehensive global assessment of the patient by the physician incorporating caregiver input), and the ADCS-ADL (Alzheimer's Disease Cooperative Study – Activities of Daily Living, a caregiver-rated assessment of the activities of daily living including personal hygiene, feeding, dressing, household chores such as shopping, retention of ability to orient oneself to surroundings as well as involvement in activities related to finances). The 24-week results for the three assessment tools are summarised in Table 2.

Table 2

ITT-LOCF population	**Rivastigmine transdermal patches 9.5 mg/24 h N = 251**	**Rivastigmine capsules 12 mg/day N = 256**	**Placebo N = 282**
ADAS-Cog			
	(n=248)	(n=253)	(n=281)
Mean baseline ± SD	27.0 ± 10.3	27.9 ± 9.4	28.6 ± 9.9
Mean change at week 24 ± SD	-0.6 ± 6.4	-0.6 ± 6.2	1.0 ± 6.8
p-value versus placebo	0.005*[1]	0.003*[1]	
ADCS-CGIC			
	(n=248)	(n=253)	(n=278)
Mean score ± SD	3.9 ± 1.20	3.9 ± 1.25	4.2 ± 1.26
p-value versus placebo	0.010*[2]	0.009*[2]	
ADCS-ADL			

	(n=247)	(n=254)	(n=281)
Mean baseline ± SD	50.1 ± 16.3	49.3 ± 15.8	49.2 ± 16.0
Mean change at week 24 ± SD	-0.1 ± 9.1	-0.5 ± 9.5	-2.3 ± 9.4
p-value versus placebo	0.013*[1]	0.039*[1]	

* p≤0.05 versus placebo
ITT: Intent-To-Treat; LOCF: Last Observation Carried Forward
[1] Based on ANCOVA with treatment and country as factors and baseline value as a covariate. Negative ADAS-Cog changes indicate improvement. Positive ADCS-ADL changes indicate improvement.
[2] Based on CMH test (van Elteren test) blocking for country. ADCS-CGIC scores <4 indicate improvement.

The results for clinically relevant responders from the 24-week placebo-controlled study are provided in Table 3. Clinically relevant improvement was defined a priori as at least 4-point improvement on the ADAS-Cog, no worsening on the ADCS-CGIC, and no worsening on the ADCS-ADL.

Table 3

	Patients with clinically significant response (%)		
ITT-LOCF population	**Rivastigmine transdermal patches 9.5 mg/24 h N = 251**	**Rivastigmine capsules 12 mg/day N = 256**	**Placebo N = 282**
At least 4 points improvement on ADAS-Cog with no worsening on ADCS-CGIC and ADCS-ADL	17.4	19.0	10.5
p-value versus placebo	0.037*	0.004*	

*p<0.05 versus placebo

As suggested by compartmental modeling, 9.5 mg/24 h transdermal patches exhibited exposure similar to that provided by an oral dose of 12 mg/day.

48-week active comparator controlled study
Patients involved in the active comparator controlled study had an initial baseline MMSE score of 10-24. The study was designed to compare the efficacy of the 13.3 mg/24 h transdermal patch against the 9.5 mg/24 h transdermal patch during a 48-week double-blind treatment phase in Alzheimer's disease patients who demonstrated functional and cognitive decline after an initial 24-48 week open-label treatment phase while on a maintenance dose of 9.5 mg/24 h transdermal patch. Functional decline was assessed by the investigator and cognitive decline was defined as a decrease in the MMSE score of ≥4 points from the previous visit or a decrease of ≥3 points from baseline. Efficacy was established by the use of ADAS-Cog (Alzheimer's Disease Assessment Scale – Cognitive subscale, a performance-based measure of cognition) and the ADCS-IADL (Alzheimer's Disease Cooperative Study – Instrumental Activities of Daily Living) assessing instrumental activities which include maintaining finances, meal preparation, shopping, ability to orient oneself to surroundings, ability to be left unattended. The 48-week results for the two assessment tools are summarised in Table 4.

Table 4

Population/Visit		**Rivastigmine 13.3 mg/24 h N = 265**		**Rivastigmine 9.5 mg/24 h N = 271**		**Rivastigmine 13.3 mg/24 h**		**Rivastigmine 9.5 mg/24 h**
		n	**Mean**	**n**	**Mean**	**DLSM**	**95% CI**	**p-value**
ADAS-Cog								
LOCF	Baseline	264	34.4	268	34.9			

	DB-week 48	Value	264	38.5	268	39.7			
		Change	264	4.1	268	4.9	-0.8	(-2.1, 0.5)	0.227
ADCS-IADL									
LOCF		Baseline	265	27.5	271	25.8			
	Week 48	Value	265	23.1	271	19.6			
		Change	265	-4.4	271	-6.2	2.2	(0.8, 3.6)	0.002*

CI – confidence interval.
DLSM – difference in least square means.
LOCF – Last Observation Carried Forward.
ADAS-cog scores: A negative difference in DLSM indicates greater improvement in Rivastigmine 13.3 mg/24 h as compared to Rivastigmine 9.5 mg/24 h.
ADCS-IADL scores: A positive difference in DLSM indicates greater improvement in Rivastigmine 13.3 mg/24 h as compared to Rivastigmine 9.5 mg/24 h.
N is the number of patients with an assessment at baseline (last assessment in the initial open-label phase) and with at least 1 post-baseline assessment (for the LOCF).
The DLSM, 95% CI, and p-value are based on an ANCOVA (analysis of covariance) model adjusted for country and baseline ADAS-cog score.
* $p<0.05$

The European Medicines Agency has waived the obligation to submit the results of studies with rivastigmine in all subsets of the paediatric population in the treatment of Alzheimer's dementia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Absorption of rivastigmine from rivastigmine transdermal patches is slow. After the first dose, detectable plasma concentrations are observed after a lag time of 0.5-1 hour. C_{max} is reached after 10-16 hours. After the peak, plasma concentrations slowly decrease over the remainder of the 24-hour period of application. With multiple dosing (such as at steady state), after the previous transdermal patch is replaced with a new one, plasma concentrations initially decrease slowly for about 40 minutes on average, until absorption from the newly applied transdermal patch becomes faster than elimination, and plasma levels begin to rise again to reach a new peak at approximately 8 hours. At steady state, trough levels are approximately 50% of peak levels, in contrast to oral administration, with which concentrations fall off to virtually zero between doses. Although less pronounced than with the oral formulation, exposure to rivastigmine (C_{max} and AUC) increased over-proportionally by a factor of 2.6 and 4.9 when escalating from 4.6 mg/24 h to 9.5 mg/24 h and to 13.3 mg/24 h, respectively. The fluctuation index (FI), a measure of the relative difference between peak and trough concentrations ($(C_{max}-C_{min})/C_{avg}$), was 0.58 for rivastigmine 4.6 mg/24 h transdermal patches, 0.77 for rivastigmine 9.5 mg/24 h transdermal patches and 0.72 for rivastigmine 13.3 mg/24 h transdermal patches, thus demonstrating a much smaller fluctuation between trough and peak concentrations than for the oral formulation (FI = 3.96 (6 mg/day) and 4.15 (12 mg/day)).

The dose of rivastigmine released from the transdermal patch over 24 hours (mg/24 h) cannot be directly equated to the amount (mg) of rivastigmine contained in a capsule with respect to plasma concentration produced over 24 hours.

The single-dose inter-subject variability in rivastigmine pharmacokinetic parameters (normalised to dose/kg bodyweight) was 43% (C_{max}) and 49% (AUC_{0-24h}) after transdermal administration versus 74% and 103%, respectively, after the oral form. The inter-patient variability in a steady-state study in Alzheimer's dementia was at most 45% (C_{max}) and 43% (AUC_{0-24h}) after use of the transdermal patch, and 71% and 73%, respectively, after administration of the oral form.

A relationship between active substance exposure at steady state (rivastigmine and metabolite

NAP226-90) and bodyweight was observed in Alzheimer's dementia patients. Compared to a patient with a body weight of 65 kg, the rivastigmine steady-state concentrations in a patient with a body weight of 35 kg would be approximately doubled, while for a patient with a body weight of 100 kg the concentrations would be approximately halved. The effect of bodyweight on active substance exposure suggests special attention to patients with very low body weight during up-titration (see section 4.4).

Exposure (AUC_∞) to rivastigmine (and metabolite NAP266-90) was highest when the transdermal patch was applied to the upper back, chest, or upper arm and approximately 20–30% lower when applied to the abdomen or thigh.

There was no relevant accumulation of rivastigmine or the metabolite NAP226-90 in plasma in patients with Alzheimer's disease, except that plasma levels were higher on the second day of transdermal patch therapy than on the first.

Distribution
Rivastigmine is weakly bound to plasma proteins (approximately 40%). It readily crosses the blood-brain barrier and has an apparent volume of distribution in the range of 1.8-2.7 l/kg.

Biotransformation
Rivastigmine is rapidly and extensively metabolised with an apparent elimination half-life in plasma of approximately 3.4 hours after removal of the transdermal patch. Elimination was absorption rate limited (flip-flop kinetics), which explains the longer $t_{½}$ after transdermal patch (3.4 h) versus oral or intravenous administrations (1.4 to 1.7 h). Metabolism is primarily via cholinesterase-mediated hydrolysis to the metabolite NAP226-90. *In vitro*, this metabolite shows minimal inhibition of acetylcholinesterase (<10%). Based on evidence from *in vitro* and animal studies, the major cytochrome P450 isoenzymes are minimally involved in rivastigmine metabolism. Total plasma clearance of rivastigmine was approximately 130 litres/h after a 0.2 mg intravenous dose and decreased to 70 litres/h after a 2.7 mg intravenous dose, which is consistent with the non-linear, over-proportional pharmacokinetics of rivastigmine due to saturation of its elimination.

The metabolite-to-parent AUC_∞ ratio was around 0.7 after transdermal patch administration versus 3.5 after oral administration, indicating that much less metabolism occurred after dermal compared to oral treatment. Less NAP226-90 is formed following application of the transdermal patch, presumably because of the lack of presystemic (hepatic first pass) metabolism, in contrast to oral administration.

Elimination
Unchanged rivastigmine is found in trace amounts in the urine; renal excretion of the metabolites is the major route of elimination after transdermal patch administration. Following administration of oral ^{14}C-rivastigmine, renal elimination was rapid and essentially complete (>90%) within 24 hours. Less than 1% of the administered dose is excreted in the faeces.

Elderly population
Age had no impact on the exposure to rivastigmine in Alzheimer's disease patients treated with rivastigmine transdermal patches.

Hepatic impairment
No study was conducted with rivastigmine transdermal patches in subjects with hepatic impairment. After oral administration, the C_{max} of rivastigmine was approximately 60% higher and the AUC of rivastigmine was more than twice as high in subjects with mild to moderate hepatic impairment than in healthy subjects.

Renal impairment
No study was conducted with rivastigmine transdermal patches in subjects with renal impairment. After oral administration, C_{max} and AUC of rivastigmine were more than twice as high in Alzheimer patients with moderate renal impairment compared with healthy subjects; however there were no changes in C_{max} and AUC of rivastigmine in Alzheimer patients with severe renal impairment.

5.3 Preclinical safety data

Oral and topical repeated-dose toxicity studies in mice, rats, rabbits, dogs and minipigs revealed only effects associated with an exaggerated pharmacological action. No target organ toxicity was observed. Oral and topical dosing in animal studies was limited due to the sensitivity of the animal models used.

Rivastigmine was not mutagenic in a standard battery of *in vitro* and *in vivo* tests, except in a chromosomal aberration test in human peripheral lymphocytes at a dose exceeding 10^4 times the foreseen clinical exposure. The *in vivo* micronucleus test was negative.

No evidence of carcinogenicity was found in oral and topical studies in mice and in an oral study in rats at the maximum tolerated dose. The exposure to rivastigmine and its metabolites was approximately equivalent to human exposure with highest doses of rivastigmine capsules and transdermal patches.

In animals, rivastigmine crosses the placenta and is excreted into milk. Oral studies in pregnant rats and rabbits gave no indication of teratogenic potential on the part of rivastigmine. Specific dermal studies in pregnant animals have not been conducted.

Rivastigmine transdermal patches were not phototoxic. In some other dermal toxicity studies, a mild irritant effect on the skin of laboratory animals, including controls, was observed. This may indicate a potential for rivastigmine transdermal patches to induce mild erythema in patients. When administered to rabbit eyes in primary eye irritation studies, rivastigmine caused reddening and swelling of the conjunctiva, corneal opacities and miosis which persisted for 7 days. Therefore, the patient/caregiver should avoid contact with the eyes after handling of the patch (see section 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Backing layer
Polyester and ethyl vinyl acetate

Drug-in-adhesive (DIA) matrix
Acrylate copolymer adhesive
Isopropyl myristate

Release liner
Polyester

6.2 Incompatibilities

To prevent interference with the adhesive properties of the transdermal patch, no cream, lotion or powder should be applied to the skin area where the medicinal product is to be applied.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Heat-sealed pouches made of paper/aluminium/acrylonitrile-methacrylate copolymer laminate. One pouch contains one transdermal patch.

Available in packs containing 7, 30, 60 and 90 pouches.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Used transdermal patches should be folded in half, with the adhesive side inwards, placed in the original pouch and discarded safely and out of the sight and reach of children.
Any used or unused transdermal patches should be disposed of in accordance with local requirements or returned to the pharmacy.

7. MARKETING AUTHORISATION HOLDER

3M Health Care Limited,
1 Morley Street,
Loughborough,
Leicestershire,
LE11 1EP
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/14/911/005
EU/1/14/911/006
EU/1/14/911/007
EU/1/14/911/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Enestia
Klöcknerstraat 1, 3930 Hamont-Achel
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where Rivastigmine 3M Health Care Ltd. is marketed, at launch and after launch of the transdermal patch all physicians who are expected to prescribe Rivastigmine 3M Health Care Ltd. are provided with an information pack containing the following elements:

- Summary of Product Characteristics
- Patient reminder card
- Instructions to provide patients and caregivers with the patient reminder card

The 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 reminder card to record patch application and removal.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine 3M Health Care Ltd. 4.6 mg/24 h transdermal patch
rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 transdermal patch of 4.15 cm^2 contains 7.17 mg rivastigmine and delivers 4.6 mg/24 h.

3. LIST OF EXCIPIENTS

Also contains polyester, ethyl vinyl acetate, acrylate copolymer adhesive and isopropyl myristate.

4. PHARMACEUTICAL FORM AND CONTENTS

7 transdermal patches
30 transdermal patches
60 transdermal patches
90 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

3M Health Care Limited,
1 Morley Street,
Loughborough,
Leicestershire,
LE11 1EP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/911/001 [7 pouches]
EU/1/14/911/002 [30 pouches]
EU/1/14/911/003 [60 pouches]
EU/1/14/911/004 [90 pouches]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rivastigmine 3M Health Care Ltd. 4.6 mg/24 h

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POUCH

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Rivastigmine 3M Health Care Ltd. 4.6 mg/24 h transdermal patch
rivastigmine
Transdermal use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch per pouch.

6. OTHER

Apply one patch per day. Take off the previous patch before putting ONE new patch on.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine 3M Health Care Ltd. 9.5 mg/24 h transdermal patch
rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 transdermal patch of 8.3 cm^2 contains 14.33 mg rivastigmine and delivers 9.5 mg/24 h.

3. LIST OF EXCIPIENTS

Also contains polyester, ethyl vinyl acetate, acrylate copolymer adhesive and isopropyl myristate.

4. PHARMACEUTICAL FORM AND CONTENTS

7 transdermal patches
30 transdermal patches
60 transdermal patches
90 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

3M Health Care Limited,
1 Morley Street,
Loughborough,
Leicestershire,
LE11 1EP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/911/005 [7 pouches]
EU/1/14/911/006 [30 pouches]
EU/1/14/911/007 [60 pouches]
EU/1/14/911/008 [90 pouches]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rivastigmine 3M Health Care Ltd. 9.5 mg/24 h

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

POUCH

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Rivastigmine 3M Health Care Ltd. 9.5 mg/24 h transdermal patch
rivastigmine
Transdermal use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch per pouch.

6. OTHER

Apply one patch per day. Take off the previous patch before putting ONE new patch on.

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

Rivastigmine 3M Health Care Ltd. 4.6 mg/24 h transdermal patch
Rivastigmine 3M Health Care Ltd. 9.5 mg/24 h transdermal patch
rivastigmine

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rivastigmine 3M Health Care Ltd. is and what it is used for

The active substance of Rivastigmine 3M Health Care Ltd. is rivastigmine.

Rivastigmine belongs to a class of substances called cholinesterase inhibitors. In patients with Alzheimer's dementia, certain nerve cells die in the brain, resulting in low levels of the neurotransmitter acetylcholine (a substance that allows nerve cells to communicate with each other). Rivastigmine works by blocking the enzymes that break down acetylcholine: acetylcholinesterase and butyrylcholinesterase. By blocking these enzymes, Rivastigmine 3M Health Care Ltd. allows levels of acetylcholine to be increased in the brain, helping to reduce the symptoms of Alzheimer's disease.

Rivastigmine 3M Health Care Ltd. is used for the treatment of adult patients with mild to moderately severe Alzheimer's dementia, a progressive brain disorder that gradually affects memory, intellectual ability and behaviour.

2. What you need to know before you use Rivastigmine 3M Health Care Ltd.

Do not use Rivastigmine 3M Health Care Ltd.
- if you are allergic to rivastigmine or any of the other ingredients of this medicine (listed in section 6).
- if you have ever had an allergic reaction to a similar type of medicine (carbamate derivatives).
- if you have a skin reaction spreading beyond the patch size, if there is a more intense local reaction (such as blisters, increasing skin inflammation, swelling) and if it does not improve within 48 hours after removal of the transdermal patch.

If this applies to you, tell your doctor and do not apply Rivastigmine 3M Health Care Ltd. transdermal patches.

Warnings and precautions
Talk to your doctor before using Rivastigmine 3M Health Care Ltd.:
- if you have, or have ever had, an irregular heartbeat.
- if you have, or have ever had, an active stomach ulcer.

- if you have, or have ever had, difficulties in passing urine.
- if you have, or have ever had, seizures.
- if you have, or have ever had, asthma or a severe respiratory disease.
- if you suffer from trembling.
- if you have a low body weight.
- if you have gastrointestinal reactions such as feeling sick (nausea), being sick (vomiting) and diarrhoea. You may become dehydrated (losing too much fluid) if vomiting or diarrhoea are prolonged.
- if you have impaired liver function.

If any of these apply to you, your doctor may need to monitor you more closely while you are on this medicine.

If you have not applied a patch for several days, do not apply the next one before you have talked to your doctor.

Use in children and adolescents
There is no relevant use of Rivastigmine 3M Health Care Ltd. in the paediatric population in the treatment of Alzheimer's disease.

Other medicines and Rivastigmine 3M Health Care Ltd.
Please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Rivastigmine 3M Health Care Ltd. might interfere with anticholinergic medicines some of which are medicines used to relieve stomach cramps or spasms (e.g. dicyclomine), to treat Parkinson's disease (e.g. amantadine) or to prevent motion sickness (e.g. diphenhydramine, scopolamine or meclizine).

If you have to undergo surgery whilst using Rivastigmine 3M Health Care Ltd. transdermal patches, tell your doctor that you are using them because they may exaggerate the effects of some muscle relaxants during anaesthesia.

Pregnancy, breast feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

If you are pregnant, the benefits of using Rivastigmine 3M Health Care Ltd. transdermal patches must be assessed against the possible effects on your unborn child. Rivastigmine 3M Health Care Ltd. should not be used during pregnancy unless clearly necessary.

You should not breast-feed during treatment with Rivastigmine 3M Health Care Ltd. transdermal patches.

Driving and using machines
Your doctor will tell you whether your illness allows you to drive vehicles and use machines safely. Rivastigmine 3M Health Care Ltd. transdermal patches may cause fainting or severe confusion. If you feel faint or confused do not drive, use machines or perform any other tasks that require your attention.

3. How to use Rivastigmine 3M Health Care Ltd.

Always use this medicine exactly as described in this leaflet and as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

IMPORTANT:
- **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 start treatment
Your doctor will tell you which Rivastigmine 3M Health Care Ltd. transdermal patch is most suitable for you.
- Treatment usually starts with Rivastigmine 3M Health Care Ltd. 4.6 mg/24 h.
- The recommended daily dose is Rivastigmine 3M Health Care Ltd. 9.5 mg/24 h. If well tolerated, the treating physician may consider increasing the dose to 13.3 mg/24 h (this high strength is currently not available from 3M but may be available from other Marketing Authorisation Holders).
- Only wear one Rivastigmine 3M Health Care Ltd. patch at a time and replace the patch with a new one after 24 hours.

During the course of the treatment your doctor may adjust the dose to suit your individual needs.

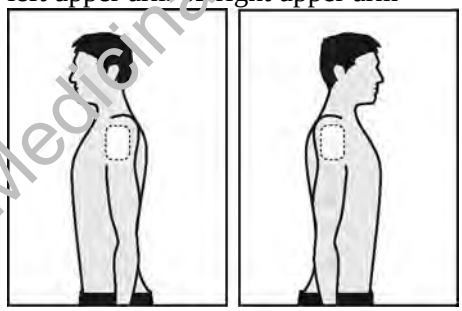
If you have not applied a patch for three days, do not apply the next one before you have talked to your doctor. Transdermal patch treatment can be resumed at the same dose if treatment is not interrupted for more than three days. Otherwise your doctor will restart your treatment on Rivastigmine 3M Health Care Ltd. 4.6 mg/24 h.

Rivastigmine 3M Health Care Ltd. can be used with food, drink and alcohol.

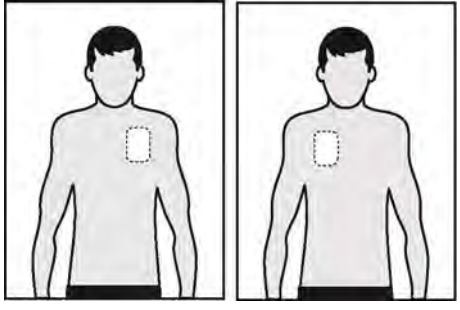
Where to apply your Rivastigmine 3M Health Care Ltd. transdermal patch
- Before you apply a patch, make sure that your skin is clean, dry and hairless, free of any powder, oil, moisturiser or lotion that could keep the patch from sticking to your skin properly, free of cuts, rashes and/or irritations.
- **Carefully remove any existing patch before putting on a new one.** Having multiple patches on your body could expose you to an excessive amount of this medicine which could be potentially dangerous.
- Apply **ONE** patch per day to **ONLY ONE** of the possible locations shown in the following diagrams:

Every 24 hours take off the previous patch before putting ONE new patch on to ONLY ONE of the following possible locations.

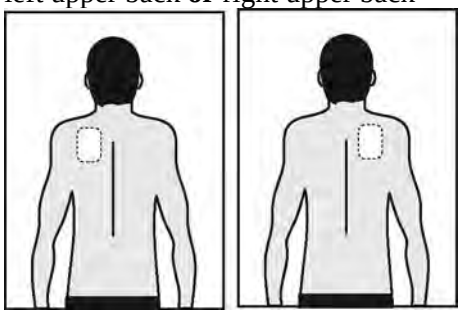
- left upper arm **or** right upper arm



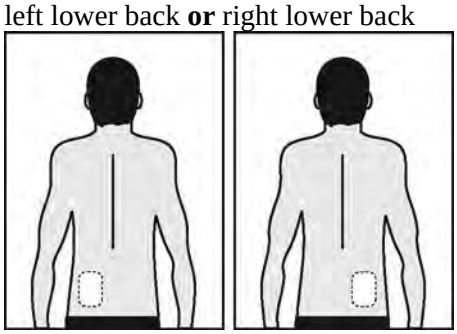
- left upper chest **or** right upper chest **(avoid breast)**



- left upper back **or** right upper back



- left lower back **or** right lower back



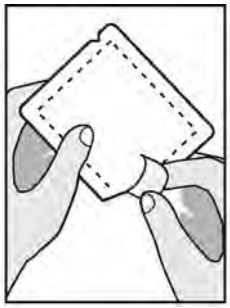
When changing the patch, you must remove the previous day's patch before you apply the new one to a different location of skin each time (for example on the right side of your body one day, then on the left side the next day, and on your upper body one day, then on your lower body the next day). Do not apply a new patch to the same skin area twice within 14 days.

How to apply your Rivastigmine 3M Health Care Ltd. transdermal patch
Rivastigmine 3M Health Care Ltd. patches are transparent to translucent, plastic patches that stick to the skin. Each patch is sealed in a pouch that protects it until you are ready to put it on. Do not open the pouch or remove a patch until just before you apply it.

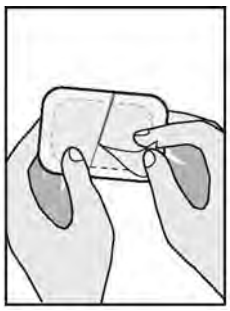
Carefully remove the existing patch before putting on a new one.

For patients starting treatment for the first time and for patients restarting Rivastigmine 3M Health Care Ltd. after treatment interruption, please begin with the second picture.

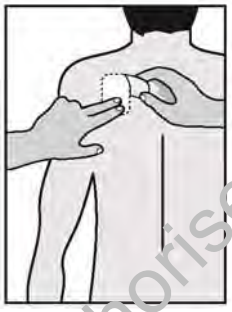
- Each patch is sealed in its own protective pouch.
  You should only open the pouch when you are ready to apply the patch.
  Tear the pouch open where indicated and remove the patch from the pouch. The pouch can be torn open in two places.



- A protective liner covers the sticky side of the patch.
  Peel off one half of the protective liner and do not touch the sticky part of the patch with the fingers.



- Put the sticky side of the patch on the upper or lower back, upper arm or chest and then peel off the second half of the protective liner.



- Then press the patch firmly in place for at least 30 seconds using the palm of the hand to make sure that the edges stick well.

If it helps you, you may write, for example, the day of the week, on the patch with a thin ball point pen.

The patch should be worn continuously until it is time to replace it with a new one. You may wish to experiment with different locations when applying a new patch, to find ones that are most comfortable for you and where clothing will not rub on the patch.

How to remove your Rivastigmine 3M Health Care Ltd. transdermal patch
Gently pull at one edge of the patch to remove it slowly from the skin. In case the adhesive residue is left over on your skin, gently soak the area with warm water and mild soap or use baby oil to remove it. Alcohol or other dissolving liquids (nail polish remover or other solvents) should not be used.

You should wash your hands with soap and water after removing the patch. In case of contact with eyes or if the eyes become red after handling the patch, rinse immediately with plenty of water and seek medical advice if symptoms do not resolve.

Can you wear your Rivastigmine 3M Health Care Ltd. transdermal patch when you are bathing, swimming, or in the sun?
- Bathing, swimming or showering should not affect the patch. Make sure the patch does not loosen during these activities.
- Do not expose the patch to any external heat sources (e.g. excessive sunlight, saunas, solarium) for long periods of time.

What to do if a patch falls off
If a patch falls off, apply a new one for the rest of the day, then replace it at the same time as usual the next day.

When and for how long to apply your Rivastigmine 3M Health Care Ltd. transdermal patch
- To benefit from treatment, you must apply a new patch every day, preferably at the same time of day.

- Only wear one Rivastigmine 3M Health Care Ltd. patch at a time and replace the patch with a new one after 24 hours.

If you use more Rivastigmine 3M Health Care Ltd. than you should
If you accidentally apply more than one patch, remove all the patches from your skin, then inform your doctor that you have accidentally applied more than one patch. You may require medical attention. Some people who have accidentally taken too much Rivastigmine 3M Health Care Ltd. have experienced feeling sick (nausea), being sick (vomiting), diarrhoea, high blood pressure and hallucinations. Slow heartbeat and fainting may also occur.

If you forget to use Rivastigmine 3M Health Care Ltd.
If you find you have forgotten to apply a patch, apply one immediately. You may apply the next patch at the usual time the next day. Do not apply two patches to make up for the one that you missed.

If you stop using Rivastigmine 3M Health Care Ltd.
Tell your doctor or pharmacist if you stop using the patch.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

You may have side effects more often when you start your medicine or when your dose is increased. Usually, the side effects will slowly go away as your body gets used to the medicine.

Take off your patch and tell your doctor straight away, if you notice any of the following side effects which could become serious:

Common (may affect up to 1 in 10 people)
- Loss of appetite
- Feeling dizzy
- Feeling agitated or sleepy
- Urinary incontinence (inability to retain adequate urine)

Uncommon (may affect up to 1 in 100 people)
- Problems with your heartbeat such as slow heartbeat
- Seeing things that are not really there (hallucinations)
- Stomach ulcer
- Dehydration (losing too much fluid)
- Hyperactivity (high level of activity, restlessness)
- Aggression

Rare (may affect up to 1 in 1,000 people)
- Falling

Very rare (may affect up to 1 in 10,000 people)
- Stiff arms or legs
- Trembling hands

Not known (frequency cannot be estimated from the available data)
- Allergic reaction where the patch was used, such as blisters or inflamed skin
- The signs of Parkinson's disease get worse – such as tremor, stiffness and shuffling
- Inflammation of the pancreas – signs include serious upper stomach pain, often with feeling sick (nausea) or being sick (vomiting)

- Fast or uneven heartbeat
- High blood pressure
- Fits (seizures)
- Liver disorders (yellow skin, yellowing of the whites of the eyes, abnormal darkening of the urine or unexplained nausea, vomiting, tiredness and loss of appetite)
- Changes in tests which show how well the liver is working
- Feeling restless

Take off your patch and tell your doctor straight away, if you notice any of the side effects above.

Other side effects seen with Rivastigmine 3M Health Care Ltd. capsules or oral solution and which may occur with the patch:

Common (may affect up to 1 in 10 people)
- Too much saliva
- Loss of appetite
- Feeling restless
- Generally feeling unwell
- Trembling or feeling confused
- Increased sweating

Uncommon (may affect up to 1 in 100 people)
- Uneven heart rate (e.g. fast heart rate)
- Difficulty sleeping
- Accidental falls

Rare (may affect up to 1 in 1,000 people)
- Fits (seizures)
- Ulcer in the intestine
- Chest pain – this may be caused by heart spasm

Very rare (may affect up to 1 in 10,000 people)
- High blood pressure
- Inflammation of the pancreas – the signs include serious upper stomach pain, often with feeling sick (nausea) or being sick (vomiting)
- Bleeding in the gut – shows as blood in stools or when being sick
- Seeing things that are not there (hallucinations)
- Some people who have been violently sick have had tearing of the tube that connects your mouth with your stomach (oesophagus)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rivastigmine 3M Health Care Ltd.

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date, which is stated on the carton and pouch after EXP. The expiry date refers to the last day of that month.
- Store in the original package in order to protect from light.
- Do not use this medicine if you see that the patch is damaged or shows signs of tampering.
- After removing a patch, fold it in half with the sticky sides on the inside and press them together. Return the used patch to its sachet and dispose of it in such a way that children cannot handle it. Do not touch your eyes with your fingers and wash your hands with soap and water

after removing the patch. If your community burns domestic rubbish, you can dispose of the patch with your domestic rubbish. Otherwise, return used patches to a pharmacy, preferably in the original packaging.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rivastigmine 3M Health Care Ltd. contains

- The active substance is rivastigmine.
  - Rivastigmine 3M Health Care Ltd. 4.6 mg/24 h transdermal patches: Each patch releases 4.6 mg of rivastigmine per 24 hours, is 4.15 cm^2 and contains 7.17 mg of rivastigmine.
  - Rivastigmine 3M Health Care Ltd. 9.5 mg/24 h transdermal patches: Each patch releases 9.5 mg of rivastigmine per 24 hours, is 8.3 cm^2 and contains 14.33 mg of rivastigmine.
- The other ingredients are polyester, ethyl vinyl acetate, acrylate copolymer adhesive and isopropyl myristate.

What Rivastigmine 3M Health Care Ltd. looks like and contents of the pack

The transdermal patches are rectangular with rounded corners, approximately 2.5 cm by 1.8 cm (Rivastigmine 3M Health Care Ltd. 4.6 mg/24 h transdermal patch) or 3.5 cm by 2.6 cm (Rivastigmine 3M Health Care Ltd. 9.5 mg/24 h transdermal patch).
Each transdermal patch consists of three layers; a backing layer, an adhesive layer containing the medicine and a transparent, split release liner. The backing layer is transparent to translucent and labelled with “R5” (Rivastigmine 3M Health Care Ltd. 4.6 mg/24 h transdermal patch) or “R10” (Rivastigmine 3M Health Care Ltd. 9.5 mg/24 h transdermal patch).

One transdermal patch is sealed in one pouch. The patches are available in packs containing 7, 30, 60 and 90 pouches. Not all pack sizes may be marketed in your country.

Marketing Authorisation Holder

3M Health Care Limited,
1 Morley Street,
Loughborough,
Leicestershire,
LE11 1EP
United Kingdom

Manufacturer

Enestia
Klöcknerstraat 1
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Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {**month YYYY**}

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu