SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Alzest 13.3 mg/24 h Transdermal Patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each transdermal patch releases 13.3 mg of rivastigmine per 24 hours. Each transdermal patch of 12.8 cm^2 contains 19.2 mg of rivastigmine.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch

Each transdermal patch is a circular, thin, matrix-type transdermal patch of diameter of approx. 4 cm consisting of four layers. The backing layer is tan coloured with orange printing “RIV-TDS 13.3 mg/24 h”.

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**
Alzest 13.3 mg/24 h	13.3 mg

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 Alzest 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 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: Due to increased exposure in mild to moderate hepatic impairment as observed with the oral formulation, dosing recommendations to titrate according to individual tolerability should be closely followed. Patients with clinically significant hepatic impairment may experience more dose-dependent adverse reactions. Patients with severe hepatic impairment have not been studied. Particular caution should be exercised in titrating these patients (see sections 4.4 and 5.2).
- Renal impairment: No dose adjustment is necessary for patients with renal impairment (see section 5.2).

Method of administration

Transdermal use

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.

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

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

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 patch 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 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 transdermal patches.

Bradycardia

Rivastigmine may cause bradycardia which constitutes a risk factor in the occurrence of torsade de pointes, predominantly in patients with risk factors. Caution is advised in patients at higher risk of developing torsade de pointes; for example, those with uncompensated heart failure, recent myocardial infarction, bradyarrhythmias, a predisposition to hypokalaemia or hypomagnesaemia, or concomitant use with medicinal products known to induce QT prolongation and/or torsade de pointes (see sections 4.5 and 4.8).

Other adverse reactions

Care must be taken when prescribing rivastigmine 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 allergic dermatitis (disseminated) 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 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 may experience more adverse reactions. Dosing recommendations to titrate according to individual tolerability must be closely followed. Patients with severe hepatic impairment have not been studied. Particular caution must be exercised in titrating these patients (see sections 4.2 and 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed with rivastigmine 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 and possible additive effects, rivastigmine should not be given concomitantly with other cholinomimetic substances. Rivastigmine might interfere with the activity of anticholinergic medicinal products (e.g. oxybutynin, tolterodine).

Additive effects leading to bradycardia (which may result in syncope) have been reported with the combined use of various beta-blockers (including atenolol) and rivastigmine. Cardiovascular betablockers are expected to be associated with the greatest risk, but reports have also been received in patients using other beta-blockers. Therefore, caution should be exercised when rivastigmine is combined with beta-blockers and also other bradycardia agents (e.g.class III antiarrhythmic agents, calcium channel antagonists, digitalis glycoside, pilocarpin).

Since bradycardia constitutes a risk factor in the occurrence of torsades de pointes, the combination of rivastigmine with torsades de pointes-inducing medicinal products such as antipsychotics i.e. some phenothiazines (chlorpromazine, levomepromazine), benzamides (sulpiride, sultopride, amisulpride, tiapride, veralipride), pimozide, haloperidol, droperidol, cisapride, citalopram, diphemanil, erythromycin IV, halofantrin, mizolastin, methadone, pentamidine and moxifloxacine should be observed with caution and clinical monitoring (ECG) may also be required.

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, 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

In pregnant animals, rivastigmine and /or metabolites crossed the placenta. It is not known if this occurs in humans. 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 in milk. It is not known if rivastigmine is excreted into human milk. Therefore, women on rivastigmine should not breast-feed.

Fertility

No adverse effects of rivastigmine were observed on fertility or reproductive performance in rats (see section 5.3). Effects of rivastigmine on human fertility are not known.

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 1,670 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, nightmares
Nervous system disorders	
Common	Headache, syncope, dizziness
Uncommon	Psychomotor hyperactivity
Very rare	Extrapyramidal symptoms
Not known	Worsening of Parkinson's disease, seizure, tremor, somnolence pleurothotonus (Pisa syndrome)
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)
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

*In a 24-week controlled study in Japanese patients, application site erythema, application site oedema and application site pruritus were reported as "very common".

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: malaise, 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 double-blind controlled clinical trials, application site reactions were mostly mild to moderate in severity. The incidence of application site skin reactions leading to discontinuation was ≤2.3% in patients treated with rivastigmine transdermal patches. The incidence of application site skin reactions leading to discontinuation was higher in the Asian population with 4.9% and 8.4% in the Chinese and Japanese population respectively.

In two 24-week double-blind, placebo-controlled clinical trials, skin reactions were measured at each visit using a skin irritation rating scale. When observed in patients treated with rivastigmine transdermal patches, skin irritation was mostly slight or mild in severity. It was rated as severe in ≤2.2% of patients in these studies and in ≤3.7% of patients treated with rivastigmine transdermal patches in a Japanese study.

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 the Yellow Card Scheme website www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 24 hours after the overdose.

Cholinergic toxicity has been reported with muscarinic symptoms that are observed with moderate poisonings such as miosis, flushing, digestive disorders including abdominal pain, nausea, vomiting and diarrhoea, bradycardia, bronchospasm and increased bronchial secretions, hyperhidrosis, involuntary urination and/or defecation, lacrimation, hypotension and salivary hypersecretion.
In more severe cases nicotinic effects might develop such as muscular weakness, fasciculations, seizures and respiratory arrest with possible fatal outcome.

Additionally there have been post-marketing cases of dizziness, tremor, headache, somnolence, confusional state, hypertension, hallucinations and malaise. Overdose with rivastigmine transdermal patch resulting from misuse/dosing errors (application of multiple patches at a time) has been reported in the post-marketing setting and rarely in clinical trials.

Management
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 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]	

* $p \leq 0.05$ 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 >2 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 patch 15 cm^2 N = 265		Rivastigmine patch 10 cm^2 N = 271		Rivastigmine patch 15 cm^2		Riva-stigmine patch 10 cm^2
		n	Mean	n	Mean	DLSM	95% Cl	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 15 cm^2 as compared to rivastigmine 10 cm^2.
ADCS-IADL scores: A positive difference in DLSM indicates greater improvement in rivastigmine 15 cm^2 as compared to rivastigmine 10 cm^2.
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.
* $p<0.05$
Source: Study D2340-Table 11-6 and Table 11-7

The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing 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 *in vitro* studies, no pharmacokinetic interaction is expected with medicinal products metabolised by the following cytochrome isoenzymes: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, CYP2C19, or CYP2B6. Based on evidence from 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.

A population pharmacokinetic analysis showed that nicotine use increases the oral clearance of rivastigmine by 23% in patients with Alzheimer's disease (n=75 smokers and 549 non-smokers) following rivastigmine oral capsule doses for up to 12 mg/day.

Special populations
Elderly
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.

Following a single 3 mg or 6 mg oral dose, the mean oral clearance of rivastigmine was approximately 46-63% lower in patients with mild to moderate hepatic impairment (n=10, Child-Pugh score 5-12, biopsy proven) than in healthy subjects (n=10).

Renal impairment
No study was conducted with rivastigmine transdermal patches in subjects with renal impairment. Based on population analysis, creatinine clearance did not show any clear effect on steady state concentrations of rivastigmine or its metabolite. No dose adjustment is necessary in patients with renal impairment (see section 4.2).

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. The major metabolite NAP226-90 also did not show a genotoxic potential.

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. In oral studies with male and female rats, no adverse effects of rivastigmine were observed on fertility or reproductive performance of either the parent generation or the offspring of the parents. Specific dermal studies in pregnant animals have not been conducted.

Rivastigmine transdermal patches were not phototoxic and considered to be a non-sensitiser. 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.
A mild eye/mucosal irritation potential of rivastigmine was identified in a rabbit study. 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

Active layer:
- poly [(2-ethylhexyl)acrylate, vinylacetate] (50:50)

Adhesive Matrix layer
- medium molecular weight polyisobutene
- high molecular weight polyisobutene
- silica colloidal anhydrous
- paraffin light liquid

Backing layer:
- polyethylene/thermoplastic resin/aluminium coated polyester film

Release liner:
- polyester film (polyethylene terephthalate) fluoropolymer-coated

Printing ink

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Keep the transdermal patch in the sachet until use.

6.5 Nature and contents of container

Child-resistant sachet made of a paper / polyethylene terephthalate / aluminium / polyacrylnitrile multilaminated foil or paper / polyethylene terephthalate / polyethylene / aluminium / polyamide multilaminated foil (LasPoID).

Each sachet contains one transdermal patch.

Available in packs containing 7, 30 or 42 sachets and in multipacks containing 60 (2 x 30), 84 (2 x 42) or 90 (3 x 30) sachets.

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 sachet and discarded safely and out of the reach and sight 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

Dr. Reddy's Laboratories (UK) Ltd.
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Milton Road,
Cambridge, CB4 0PE,
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