SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Rivastigmine Crescent 9.5 mg/24h transdermal patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Rivastigmine Crescent 9.5 mg/24h transdermal patch
Each transdermal patch releases 9.5 mg rivastigmine per 24 hours. Each transdermal patch in the size of 10.5 cm^2 contains 18 mg rivastigmine.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch
Rivastigmine Crescent 9.5 mg/24h transdermal patch
The patch is a thin, transdermal patch of the matrix type consisting of three layers. The outer side of the backing layer is translucent and labelled in black ink with “rivastigmine” and “9.5 mg/24h”.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated for the symptomatic treatment of mild to moderate 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. The diagnosis must be made according to the currently valid guidelines. Like every 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.
<u>Posology</u>

Transdermal patch	**Rivastigmine release within 24 hours *in vivo***
Rivastigmine Crescent 4.6 mg/24h transdermal patch	4.6 mg
Rivastigmine Crescent 9.5 mg/24h transdermal patch	9.5 mg

Initial dose

The treatment is started with Rivastigmine 4.6 mg/24h.

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 the daily recommended effective dose of 9.5 mg/24h. This 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. This should be continued for as long as the patient continues to demonstrate therapeutic benefit. If well tolerated and only after a minimum treatment time of six months at 9.5 mg/24h, the treating physician may consider increasing the dose to 13.3 mg/24h in patients who have demonstrated a substantial cognitive deterioration (e.g. decrease in the MMSE) and/or functional decline (based on a physician's assessment) while they were 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. A discontinuation should be considered when there is no longer any evidence of a therapeutic effect at the optimal dose.

Treatment should be temporarily interrupted if gastrointestinal side effects are observed until the symptoms resolve. If the interruption did not last longer than three days, the treatment with the transdermal patch can be continued at the same dose. Otherwise treatment should be re-initiated with 4.6 mg/24h.

Switching from capsules or oral solution to transdermal patches

Based on comparable exposure between oral and transdermal rivastigmine (see section 5.2), patients previously treated with rivastigmine capsules or oral solution can be switched to Rivastigmine transdermal patches according to the following schedule:

- Patients on a dose of 3 mg/day oral rivastigmine can be switched to 4.6 mg/24h transdermal patches.
- Patients on a dose of 6 mg/day oral rivastigmine can be switched to 4.6 mg/24h transdermal patches.
- Patients on a stable and well tolerated dose of 9 mg/day oral rivastigmine can be switched to 9.5 mg/24h transdermal patches. If the oral dose of 9 mg/day has not been stable and well tolerated, a switch to 4.6 mg/24h transdermal patches is recommended.
- Patients on a dose of 12 mg/day oral rivastigmine can be switched to 9.5 mg/24h transdermal patches.

After switching to 4.6 mg/24h transdermal patches, and provided that these are well tolerated after a minimum of four weeks of treatment, the dose should be increased to 9.5 mg/24h, which is the recommended effective dose.
It is recommended to apply the first transdermal patch on the day after the last oral dose.

Special populations

- Paediatric population: There is no relevant benefit of rivastigmine in children and adolescents in the therapeutic area of Alzheimer's dementia.
- Patients with body weight below 50 kg: Particular caution should be exercised in patients weighing less than 50 kg when titrating the dose above the recommended effective dose of 9.5 mg/24h (see section 4.4). These patients may experience more side effects and may be more likely to discontinue the treatment due to adverse reactions.
- Hepatic impairment: Due to the increased exposure in mild to moderate hepatic impairment that has also been observed with the oral dosage forms, the recommendations for dose titration should be strictly followed according to individual tolerance. Patients with clinically significant hepatic impairments can experience more dose-dependent side effects. Patients with severe hepatic impairment have not been studied. Special caution must be exercised when 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 patches should be applied once a day to clean, dry, hairless, unbroken healthy skin on the upper or lower back, upper arm or chest, in a place that will not be affected by rubbing of tight clothing. It is not recommended to apply the transdermal patch to the thigh or to the abdomen due to decreased bioavailability of rivastigmine in these areas.
Do not apply the transdermal patch to skin that is red, irritated or injured. To minimise the potential risk of skin irritations the patch should not be applied to the same area of the body within 14 days.

Patients and caregivers should be instructed on important instructions for use:

- The patch from the previous day must be removed every day before a new patch is being applied (see section 4.9).
- After 24 hours the patch must be replaced through a new one. 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 comes off, apply a new one for the rest of the day. On the following day, replace it at the usual time.
- The patch can be worn in everyday situations, including showering/bathing and during hot weather.
- The patch should not be exposed to any external heat sources (e.g. excessive sunlight, saunas, solarium) for extended periods of time.
- The patch should not be cut into pieces.

4.3 Contraindications

This medicinal product must not be used in patients with a known hypersensitivity to the active substance rivastigmine or to other carbamate derivates or any of the excipients listed in section 6.1.
History of reactions at the application site suggestive of allergic contact dermatitis with rivastigmine patches (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 the treatment is interrupted for more than three days, it should be re-initiated with 4.6 mg/24h.
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 events; in some cases hospitalisation was required and in rare cases they led to death (see section 4.9). The most common misuse of the medicinal product and dosing errors were 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 advised on important instructions for use 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 side effects are more common in women. Patients who show signs or symptoms of dehydration resulting from prolonged vomiting or diarrhoea can be managed with intravenous fluids and a dose reduction or discontinuation if recognised and treated promptly. Dehydration can have severe consequences.
Weight loss
Patients with Alzheimer's disease may lose weight whilst taking cholinesterase inhibitors, including rivastigmine. During the treatment with rivastigmine the patients' weight should be monitored.
Other adverse reactions
Care must be taken when prescribing rivastigmine transdermal patches in the following cases:

- Patients with sick sinus syndrome or conduction defects (sinoatrial or atrioventricular block) (see section 4.8);
- to patients with active gastric or duodenal ulcers or patients with a predispositions for these conditions because rivastigmine may cause increased gastric secretions (see section 4.8);
- Patients with a tendency for urinary obstruction and seizures because cholinomimetics may induce or exacerbate these;
- Patients with a history of asthma or obstructive pulmonary disease.

Skin reactions at the application site

Rivastigmine patches can cause skin reactions at the application site that are usually mild or moderate in intensity. Patients and caregivers should be instructed accordingly.

These reactions by themselves are not yet a sign for a sensitisation. However, the use of rivastigmine patches may lead to allergic contact dermatitis.

Allergic contact dermatitis should be considered if the reactions at the application site spread beyond the patch size, if there are signs of a more intense local reaction (e.g. increasing erythema, oedema, blistering) and if symptoms do not significantly improve within 48 hours after removing the patch. In such cases the treatment should be discontinued (see section 4.3).

Patients who develop reactions at the application site that are suggestive of allergic contact dermatitis to rivastigmine patches 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 who have become sensitised to rivastigmine through the exposure to the rivastigmine patches may not be able to take rivastigmine in any form.

There have been rare post-marketing reports of patients with allergic dermatitis (disseminated) after the administration of rivastigmine irrespective of the route of administration (oral, transdermal). In these cases the treatment should be discontinued (see section 4.3).

Other warnings and precautions

Rivastigmine can exacerbate or induce extrapyramidal symptoms.

Rivastigmine may cause bradycardia which is a risk factor for the occurrence of torsade de pointes, especially in patients with risk factors. Caution is advised in patients with an increased risk of developing torsade de pointes, such as those with uncompensated heart failure, recent myocardial infarction, bradyarrhythmias, a predisposition to hypokalaemia or hypomagnesaemia or with concomitant medication known to cause QT prolongation and/or torsade de pointes (see sections 4.5 and 4.8).

After using a rivastigmine transdermal patch contact with the eyes should be avoided (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 turn red after handling the patch, rinse immediately with plenty of water and seek medical advice if symptoms do not resolve.

Special populations

- Patients with a body weight below 50 kg may experience more adverse reactions and may be more likely to discontinue the treatment due to side effect (see section 4.2). In these patients the dose must be carefully titrated and the need to be monitored for adverse reactions (e.g. excessive nausea or vomiting). In case such adverse reactions occur, it should be considered to reduce the maintenance dose to the 4.6 mg/24h transdermal patch.
- Patients with hepatic impairment: Patients with clinically significant hepatic impairments might experience more adverse reactions. The recommendations for dose titration should be strictly followed according to individual tolerance. Patients with severe hepatic impairment have not been studied. Special caution must be exercised when 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 muscle relaxants of the succinylcholine type during anaesthesia. Caution must be exercised when selecting anaesthetic agents. Possible dose adjustments or temporarily stopping treatment can be considered if needed.

Due to its pharmacodynamic effects and potential additive effects, rivastigmine should not be given concomitantly with other cholinomimetic substances. An impact of rivastigmine on the effect of anticholinergic medicinal products cannot be excluded (e.g. oxybutynin, tolterodine).

Additive effects have been reported that the combined use of various beta-blockers (including atenolol) and rivastigmine can lead to bradycardia (possibly resulting in syncope). Cardiovascular betablockers are associated with the highest risk but there have been reports about patients using other beta-blockers in this regard. Caution is therefore advised when rivastigmine is used together with beta-blockers and other bradycardia-inducing agents (e.g. class III antiarrhythmics, calcium channel antagonists, digitalis glycoside, pilocarpine).

As bradycardia is a risk factor for the occurrence of torsade de pointes, the combination of rivastigmine with other torsade de pointes-inducing drugs, such as antipsychotic agents, e.g. some phenothiazines (chlorpromazine, levomepromazine), benzamides (sulpiride, sultopride, amisulpride, tiapride, veralipride), pimozide, haloperidol, droperidol, cisapride, citalopram, diphemanil, erythromycin IV, halofantrine, mizolastine, methadone, pentamidine and moxifloxacin, should be observed with caution and clinical monitoring (ECG) may also be required.

In studies with healthy subjects no pharmacokinetic interactions have been observed between oral rivastigmine and digoxin, warfarin, diazepam or fluoxetine. The prolonged prothrombin time under warfarin is not affected by oral rivastigmine. No adverse effects on cardiac conduction were observed following concomitant administration of digoxin and oral rivastigmine.

The concomitant administration of rivastigmine and commonly prescribed medications such as antacids, antiemetics, antidiabetics, centrally acting antihypertensives, calcium antagonists, inotropic agents, angina pectoris therapies, non-steroidal anti-inflammatory drugs, oestrogens, analgesics, benzodiazepines and antihistamines was not associated with changes in the kinetics of rivastigmine or an increased risk of clinically relevant adverse effects.

Due 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 its metabolites crossed the placental barrier. 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 it is clearly necessary.

Breast-feeding

In animals, rivastigmine is excreted into the breast milk. It is not known if rivastigmine is excreted into human milk and therefore, women on rivastigmine should not breast-feed.

Fertility

No effects on fertility or reproductive performance were observed in rats under rivastigmine (see section 5.3). There are no known effects of rivastigmine on the fertility in humans.

4.7 Effects on ability to drive and use machines

Alzheimer's disease can gradually lead to an impairment of the ability to drive or compromise the ability to use machines. Furthermore, rivastigmine may case syncope and delirium. Hence, rivastigmine has minor or moderate influence on the ability to drive and use machines. Therefore, in patients with dementia treated with rivastigmine, the ability continue driving or to operate complex machines should be routinely evaluated by the treating physician.

4.8 Undesirable effects

Summary of the safety profile

Skin reactions at the application site (usually mild to moderate erythema at the application site) are the most common adverse reactions that have been observed with the use of rivastigmine transdermal patch. The next most common side effects are gastrointestinal in nature, including nausea and vomiting.

Adverse reactions in table 1 are listed according to MedDRA system organ class and frequency category.

The assessment of side effects is based on the following frequency specifications:

Very Common	(≥1/10)
Common	(≥1/100,<1/10)
Uncommon	(≥1/1,000,<1/100)
Rare	(≥1/10,000,<1/1,000)
Very rare	(<1/10,000)
Not known	(frequency cannot be estimated from the available data)

Table with an overview over side effects

Table 1 lists the adverse drug reactions that occurred in 1,670 Alzheimer's disease patients who were treated in randomised, double-blind, placebo- and drug-controlled clinical trials evaluating rivastigmine transdermal patches for 24 to 48 weeks, and from post-marketing data.

Table 1

Infections and infestations	
Common:	Urinary tract infections
Metabolic and nutritional disorders	
Common:	Lack of appetite, 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:	High blood pressure
Gastrointestinal disorders	
Common:	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain
Uncommon:	Stomach ulcer
Not known:	Pancreatitis
Hepatobiliary disorders	
Not known:	Hepatitis, elevated liver function values
Diseases of the skin and the subcutaneous tissue	
Common:	Rash
Not known:	Pruritus, erythema, urticaria, skin vesicles, allergic dermatitis (disseminated)
Renal and urinary disorders	
Common:	Urinary incontinence
General disorders and administration site conditions	
Common:	Skin reactions at the application site (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 loss
Rare:	Falls

*In a 24-week controlled study with Japanese patients, application site erythema, application site oedema, and application site pruritus were reported very frequently.

Description of selected adverse events

When doses higher than 13.3 mg/24h were used in the above-mentioned placebo-controlled study, insomnia and cardiac failure were observed more frequently than with 13.3 mg/24h or placebo, suggesting a dose effect relationship. However, with rivastigmine 13.3 mg/24h transdermal patch the events did not occur more frequently 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: Feeling unwell, confusion, increased sweating (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 the reactions at the application site were mostly mild to moderate. Skin reactions at the application site that led to a discontinuation of the study of patients who were treated with rivastigmine transdermal patch occurred in a frequency of ≤2.3%. The frequency of skin reactions at the application site that resulted in a discontinuation was higher in the Japanese population (8.4%) than in the Chinese population (4.9%).

In two 24-week double-blind, placebo-controlled clinical trials skin reactions were measured at each visit using a skin irritation scale.

In patients treated with rivastigmine transdermal patch it was observed that the skin reactions were mostly negligible or mild. In these studies, they were categorised as severe in ≤2.2% of the patients and in a Japanese study in ≤3.7% of the patients who had been treated with rivastigmine transdermal patch.

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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple 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 with muscarinic symptoms has been reported and was associated with moderate signs of intoxication such as miosis, flushing, indigestion including abdominal pain, nausea, vomiting and diarrhoea, bradycardia, bronchospasm and increased bronchial secretions, hyperhidrosis, involuntary urination and/or defecation, lacrimation, hypotension and increased salivation.

In more severe cases, nicotinic effects may develop, such as muscle weakness, fasciculations, seizures and respiratory arrest with possible fatal outcome.

Furthermore, post-marketing there have been cases of dizziness, tremor, headache, drowsiness, confusion, high blood pressure, hallucinations and feeling unwell. Overdose with rivastigmine transdermal patches resulting from misuse/dosing errors (simultaneous application of multiple patches) has been reported in the post-marketing setting and rarely in clinical trials.

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 transdermal patches should be removed immediately and no further transdermal patch should be applied for the next 24 hours. If the overdose is accompanied by severe nausea and vomiting, the use of antiemetics should be considered. Other undesired effects should be treated symptomatically as necessary.

Atropine can be administered in the event of a massive overdose. Initially, 0.03 mg/kg intravenous atropine sulphate is recommended, additional dosing should be based on the clinical response. The 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, that is expected to facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by functionally intact cholinergic neurones. Therefore, rivastigmine may have an ameliorative effect on cholinergic-mediated cognitive deficits in dementia associated with Alzheimer’s disease.

Rivastigmine forms a covalent bond with its target enzymes, which temporarily inactivates the enzymes. In healthy young male volunteers, an oral dose of 3 mg decreases the acetylcholinesterase (AChE) activity in CSF by approximately 40% within the first 1.5 hours after administration. About 9 hours after reaching the maximum inhibitory effect, the activity of the enzyme returns to the initial values. In patients with Alzheimer’s disease, inhibition of AChE in CSF by oral rivastigmine was dose-dependent up to the hightest dose tested, i.e. 6 mg administered twice daily.

The inhibition of butyrylcholinesterase activity in the cerebrospinal fluid of 14 Alzheimer's patients treated with oral rivastigmine was similar to the inhibition of AChE activity.

Clinical trials on Alzheimer's dementia

The efficacy of rivastigmine transdermal patches in patients with Alzheimer’s dementia has been investigated in a 24-week double-blind, placebo-controlled pivotal study and a subsequent open-label extension phase and in a 48-week double-blind comparison study.

24-week placebo-controlled study

The patients participating in the placebo-controlled study had an MMSE score (Mini-Mental State Examination) between 10 and 20. Efficacy was established with independent measurement tools that were used regularly during the 24-week treatment period. These tools included 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 everyday activities including personal hygiene, feeding, dressing, household chores such as shopping, maintaining the ability to orient oneself and dealing with financial matters). The results of all three measuring procedures after 24 weeks are summarised in table 2.

Table 2

ITT-LOCF-Population	**Rivastigmine 9.5 mg/24h transdermal patch N = 251**	**Rivastigmine capsules 12 mg/day N = 256**	**Placebo N = 282**
ADAS-Cog	(n = 248)	(n = 253)	(n = 281)
Mean baseline value ± SD	27.0 ± 10.3	27.9 ± 9.4	28.6 ± 9.9
Mean change after 24 weeks ± 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 value ± 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 value ± SD	50.1 ± 16.3	49.3 ± 15.8	49.2 ± 16.0
Mean change after 24 weeks ± 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] ANCOVA with the factors treatment and country and the baseline value as a covariate. Negative ADAS-Cog changes indicate improvement. Positive ADCS-ADL changes indicate improvement.

[2] CMH test (van Elteren test) with block formation by 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 a 4-point improvement on the ADAS-Cog scale, no worsening on the ADCS-CGIC, and no worsening on the ADCS-ADL.

Table 3

	Patients with clinically significant response (%)		
ITT-LOCF-Population	**Rivastigmine 9.5 mg/24h transdermal patch 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*	

* $p \leq 0.05$ versus placebo

As the model produced with compartmental modelling shows, transdermal patches releasing 9.5 mg/24h lead to a drug exposure similar to an oral dose of approximately 12 mg/day.

48-week active controlled comparison study

Patients participating in the active controlled comparison study had an initial MMSE score between 10 and 24. The of the trial of the trial was the comparison of the efficacy of the 13.3 mg/24 h transdermal patch versus the 9.5 mg/24h transdermal patch in a 48-week double-blind treatment phase in Alzheimer patients who showed a functional and cognitive decline after an initial 24-48 week open-label treatment phase while on a maintenance dose of 9.5 mg/24h transdermal patch. The functional decline was assessed by the investigator and the cognitive decline was defined as a decrease of the MMSE score by >2 points compared to the previous visit or a decrease by >3 points versus the baseline value.

Efficacy was assessed with the ADAS-Cog (Alzheimer's Disease Assessment Scale – Cognitive subscale, a performance-based tool to measure of cognition) and the ADCS-IADL (Alzheimer's Disease Cooperative Study – Instrumental Activities of Daily Living) assessing instrumental activities such as handling finances, preparing meals, shopping, orientation skills and the ability to be remain unsupervised. The results of the two measuring procedures after 48 weeks are summarised in table 4.

Table 4

Population/Visit			**Rivastigmine 15 cm² N = 265**		**Rivastigmine 10 cm² N = 271**		**Rivastigmine 15 cm²**		**Rivastigmine 10 cm²**
			n	**Mean**	**n**	**Mean**	**DLSM**	**95% CI**	**p-value**
ADAS-Cog									
LOCF	DB-week 48	Baseline value	264	34.4	268	34.9			
		Score	264	38.5	268	39.7			
		Change	264	4.1	268	4.9	-0.8	(-2.1; 0.5)	0.227
ADCS-IADL									
LOCF	Week 48	Baseline value	265	27.5	271	25.8			
		Score	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 shows a bigger improvement for rivastigmine 15 cm^2 compared to rivastigmine 10 cm^2.
ADCS-IADL scores: A positive difference in DLSM shows a bigger improvement for rivastigmine 15 cm^2 compared to rivastigmine 10 cm^2.
N is the number of patients with an evaluation of the baseline value (last assessment in the initial open phase) and with at least 1 assessment after the baseline value (for LOCF).
DLSM, 95% CI, and p-value are based on the ANCOVA (analysis of the covariance) model that was adjusted for the country and the baseline value of the 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 rivastigmine in all subsets of the paediatric population in Alzheimer's dementia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
The absorption of rivastigmine from the rivastigmine transdermal patches is slow. After the first dose, detectable plasma concentrations are observed after a lag time of 0.5-1 hour. The 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. After repeated administration (as in the steady state), the plasma level initially decreases slightly for an average of 40 minutes after changing the transdermal patch. Subsequently, the newly applied transdermal patch absorbs more active substance that is eliminated, and plasma levels increase again to reach a new peak after approximately eight hours. At steady state, the minimum level is approximately 50% of the peak level. When taken orally, however, the concentration falls to almost zero between two administrations. While the exposure to rivastigmine (C_{max} and AUC) rose less with the dose increase from 4.6 mg/24h to 9.5 mg/24h or to 13.3 mg/24h than with the oral formulation, it nevertheless increased disproportionately by a factor of 2.6 and 4.9. 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/24h transdermal patches, 0.77 for rivastigmine 9.5 mg/24h transdermal patches and 0.72 for rivastigmine 13.3 mg/24h 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/24h) cannot be directly compared to the amount (mg) of rivastigmine contained in a capsule with respect to plasma concentration produced over 24 hours.
The interindividual variability of pharmacokinetic parameters after a single dose of rivastigmine (based on dose/kg body weight) was 43% (C_{max}) and 49%

(AUC_{0-24h}) for the transdermal patch and 74% and 103% after ingestion. The variability between individual patients 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 dose.

In Alzheimer's patients, a correlation between drug exposure in the steady-state (rivastigmine and its metabolite NAP226-90) and body weight was also observed. Compared to a patient weighing 65 kg, the rivastigmine concentration at steady-state would be about doubled in a patient weighing 35 kg and halved in patient weighing 100 kg. The effect of the bodyweight on the active substance exposure suggests that special attention is required for patients with a very low body weight during up-titration (see section 4.4).

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

No relevant accumulation of rivastigmine or the metabolite NAP226-90 could be observed in the plasma of patients with Alzheimer's disease, except that plasma levels were higher on the second day in the group receiving the transdermal patch therapy than on the first.

Distribution

Rivastigmine is weakly bound to plasma proteins (approximately 40%). It easily 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; the apparent elimination half-life from plasma after removal of the transdermal patch is around 3.4 hours. Elimination is limited by the rate of absorption (flip-flop kinetics), which also explains why the t½ after application of the transdermal patch (3.4 h) is longer than after oral or intravenous administration (1.4-1.7 h). Metabolisation occurs mainly via cholinesterase-mediated hydrolysis to the metabolite NAP226-90. *In-vitro*, the metabolite shows minimal inhibition effect on acetylcholinesterase (<10%). *In-vitro* results suggest no pharmacokinetic interaction with drugs metabolised by the following cytochrome isoenzymes: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, CYP2C19, or CYP2B6. Studies with animal models show only a very low involvement of the most important cytochrome P450 isoenzymes in the metabolisation of rivastigmine. The total plasma clearance of rivastigmine is approximately 130 L/h after an intravenous dose of 0.2 mg and it decreased to 70 L/h after an intravenous dose of 2.7 mg. This decrease is consistent with the non-linear, disproportional pharmacokinetics of rivastigmine due to saturation of its elimination pathways. The AUC∞ ratio of metabolite to parent was 0.7 for transdermal patch application versus 3.5 after oral administration, indicating that the metabolism was significantly lower after dermal application than after oral administration. Less NAP226-90 is formed following the application of the transdermal patch compared to oral administration, presumably because of the lacking presystemic metabolism (hepatic first pass).

Elimination

Traces of rivastigmine are excreted unchanged in the urine; the main route of elimination after the application of the transdermal patch is the renal excretion

of the metabolites. After the oral administration of ^{14}C-rivastigmine, renal elimination occurs rapidly and nearly completely (>90%) within 24 hours. Less than 1% of the administered dose is excreted via the faeces.
A pharmacokinetic population analysis revealed that in patients with Alzheimer's disease (n=75 smokers and 549 non-smokers), nicotine consumption increases the oral rivastigmine clearance by 23% after taking oral doses of rivastigmine (capsule) of up to 12 mg/day.
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 in patients with mild to moderate hepatic impairment was approximately 60% higher and the AUC of rivastigmine was more than twice as high than in healthy subjects.
After a single dose of 3 mg or 6 mg, the mean oral clearance of rivastigmine in patients with mild to moderately renal impairment (n=10, Child-Pugh criteria 5-12, demonstrated through biopsy) was approximately 46-63 % lower than in healthy volunteers (n=10).
Renal impairment
No study was conducted with rivastigmine transdermal patches in subjects with renal impairment. Based on population analyses, creatinine clearance showed no clear effects on the steady-state concentration of rivastigmine or its metabolites. No dose adjustment is necessary for patients with renal impairment (see section 4.2).

5.3 Preclinical safety data

In toxicity studies with mice, rats, rabbits, dogs and minipigs severely exaggerated pharmacological effects were observed after repeated oral and topical administration. Organ specific toxicity did not occur. Due to the high sensitivity of the animal species used, oral and topical dosing was limited in these studies.
Rivastigmine proved to be non-mutagenic in a series of standard *in vitro* and *in vivo* tests, except in a chromosome aberration test in human peripheral lymphocytes at doses exceeding 10^4 times the maximum doses used in the clinic. The *in vivo* micronucleus test was negative. The major metabolite NAP226-90 also did not show 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 dermatologic studies in pregnant animals have not been conducted.
Rivastigmine transdermal patches were not phototoxic and considered to be a non-sensitiser. In some other dermatologic toxicity studies, a mild irritation of 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

Backing sheet
Poly(ethylen terephthalate)

Adhesive matrix I for the medicinal product
Polyacrylate
Ammonio methacrylate-copolymer (type B)

Adhesive matrix II for the medicinal product
Polyacrylate

Release-controlling layer
Poly(ethylen terephthalate), siliconised

Printing ink
Black printing ink

6.2 Incompatibilities

To ensure the adhesiveness of the transdermal patch, prior to its application no creams, lotions or powders should be applied to the area.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Do not store above 25°C.
Keep the transdermal patch in the sachet until use, in order to protect from light.

6.5 Nature and contents of container

The child-resistant sachets made of a multi-laminated composite material made of paper/PETP/aluminium/COC.
Each sachet contains a transdermal patch.
The sachet are packed in an outer box.
Available in packs containing 7, 30 or 42 sachets and in multipacks with 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

After use, the transdermal patches should be folded in half (adhesive side inwards), placed in the packaging sachet and disposed of safely, out of sight and reach of children. Used and unused transdermal patches should be disposed of in accordance with local requirements or returned to the pharmacist.

7 MARKETING AUTHORISATION HOLDER

Crescent Pharma Limited
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Sarum Hill Basingstoke
RG21 8SR
United Kingdom

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PL 20416/0970

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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