Rivacure Patch
(Rivastigmine)

Description:
Rivacure Patch 5:
5 cm^2 patch attached with quadrangle beige color protection film and release paper on adhesive layer.

Rivacure Patch 10:
10 cm^2 patch attached with quadrangle beige color protection film and release paper on adhesive layer.

Composition:
Rivacure Patch 5:
Each patch of 5 cm^2 contains 9 mg rivastigmine base, *in vivo* release rate of 4.6 mg/24 hours.

Rivacure Patch 10:
Each patch of 10 cm^2 contains 18 mg rivastigmine base, *in vivo* release rate of 9.5 mg/24 hours.

Pharmaceutical Form:
Transdermal Patch

Pharmacodynamics:
Pharmacotherapeutic group: brain-selective cholinesterase inhibitor; ATC-code: N06DA03.
Pathological changes in dementia such as Alzheimer's Disease involve cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. These pathways are known to be involved in attention, learning and memory and other cognitive processes.

Rivastigmine, a brain-selective acetyl- and butyryl-cholinesterase inhibitor of the carbamate type, is thought to facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by functionally intact cholinergic neurons. Data from animal studies indicate that rivastigmine selectively increases the availability of acetylcholine in the cortex and hippocampus. Thus, rivastigmine may have an ameliorative effect on cholinergic-mediated cognitive deficits associated with Alzheimer's Disease and with Parkinson's disease. In addition, there is some evidence that cholinesterase inhibition could slow the formation of amyloidogenic beta-amyloid-precursor protein (APP) fragments, and thus of amyloid plaques, which are one of the main pathological features of Alzheimer's Disease.
Rivastigmine interacts with its target enzymes by forming a covalently bound complex that temporarily inactivates the enzymes.

Pharmacokinetics:
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. Cmax 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 (Cmax 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 ((Cmax-Cmin)/Cavg), 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% (Cmax) and 49% (AUC0-24h) 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% (Cmax) and 43% (AUC0-24h) 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.

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 t½ 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%).

No pharmacokinetic interaction is expected with medicinal products metabolised by the following

cytochrome isoenzymes: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, CYP2C19, or CYP2B6. It was found that 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 14C-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.

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

Hepatic impairment
After oral administration, the Cmax of rivastigmine was approximately 60% higher and the AUC of rivastigmine was more than twice as high in those who are with mild to moderate hepatic impairment than in those who are healthy.
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 those who are healty (n=10).

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.

Indication:
Treatment of patients with:
- Mild to moderately severe dementia of the Alzheimer’s type,
- Severe dementia of the Alzheimer’s type,
- Mild to moderately severe dementia associated with Parkinson’s disease.

Dosage and Administration:

Recommended Dosage:
Posology

Transdermal patches	**Rivastigmine Content per patch**	**Rivastigmine *in vivo* release rates per 24 h**
Rivacure Patch 5	9 mg	4.6 mg
Rivacure Patch 10	18 mg	9.5 mg

Mild to moderately severe dementia of the Alzheimer's type
Mild to moderately severe dementia associated with Parkinson's disease
Initial dose and dose titration to the effective dose:
Treatment is started with Rivacure Patch 5 once a day. After a minimum of four weeks of treatment and if well tolerated, this dose should be increased to Rivacure Patch 10, the recommended effective dose which can be continued for as long as a therapeutic benefit for the patient exists.
Individual responses to rivastigmine may vary and some patients may derive additional benefit from higher doses

Severe dementia of the Alzheimer's type
Initial dose and dose titration to the effective dose:
Treatment is started with Rivacure Patch 5 once a day. Subsequently the dose should be increased to Rivacure Patch 10 which is the demonstrated effective dose. These dose increases should always be based on good tolerability of the current dose and may be considered only after a minimum of four weeks of treatment at each dose level.

Interruption of treatment:
Treatment should be temporarily interrupted if gastrointestinal adverse effects and/or worsening of existing extrapyramidal symptoms (e.g. tremor) are observed until these adverse effects resolve. 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 Rivacure Patch 5.
If adverse effects persist on re-initiation of therapy, the dose should be temporarily reduced to the previous well-tolerated dose.

Switching from capsules or oral solution:

Patients treated with rivastigmine capsules or oral solution may be switched to Rivacure patches as follows:
A patient who is on a dose of < 6 mg per day oral rivastigmine can be switched to Rivacure Patch 5.
A patient who is on a stable and well tolerated dose of 9 mg per day oral rivastigmine can be switched to Rivacure Patch 10. If the oral dose of 9 mg per day has not been stable and well tolerated, a switch to Rivacure Patch 5 is recommended.
It is recommended to apply the first patch on the day following the last oral dose.

Special population
Patients with body weight below 50 kg
Particular caution should be exercised in titrating patients with body weight below 50kg above the recommended effective dose Rivacure Patch 10. 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

Renal impairment
No dose adjustment is necessary for patients with renal impairment

Paediatric patients
Children and adolescents (age below 18 years): Rivastigmine is not recommended for use in children.

Method of administration

Rivacure 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. The patch should be replaced by a new one after 24 hours.

Important administration instructions (patients and caregivers should be instructed)
The previous day's patch must be removed before applying a new one.

The patch should be replaced by a new one after 24 hours. Only one patch should be worn at a time.

The patch should not be applied to skin that is red, irritated or cut. It is recommended to change the application site daily to avoid potential irritation, although consecutive patches can be applied to the same general anatomic site (e.g., another spot on the upper back).

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.

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.

Contraindication:

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 list. Previous history of application site reactions suggestive of allergic contact dermatitis with rivastigmine patch.

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/24h.

Warning and Precautions:

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. 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.

Gastrointestinal disorders

Gastrointestinal disorders such as nausea, vomiting and diarrhea are dose-related, and may occur when initiating treatment and/or increasing the dose. These adverse reactions occur more commonly in women. Patients who show signs or symptoms of dehydration resulting from prolonged vomiting or diarrhea 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.

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).

• to patients with active gastric or duodenal ulcers or patients predisposed to these conditions because rivastigmine may cause increased gastric secretions.

• 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.

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.

Other warnings and precautions
Rivastigmine may exacerbate or induce extrapyramidal symptoms.
Contact with the eyes should be avoided after handling Rivastigmine transdermal patches. 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. 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. Particular caution must be exercised in titrating these patients

Interactions with other Medicaments:
No specific interaction studies have been conducted with rivastigmine patches.
Rivastigmine is metabolised mainly through hydrolysis by esterases. Minimal metabolism occurs via the major cytochrome P450 isoenzymes thus, no pharmacokinetic interactions are anticipated with other drugs metabolised by these enzymes

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.

Side Effects:
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.

Undesirable effects
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.

Tabulated list of adverse reactions.

Infections and infestations	
Common	Urinary tract infection
Metabolism and nutrition disorders	
Common	Anorexia, decreased appetite
Uncommon	Dehydration
Psychiatric disorders	
Common Uncommon	Anxiety, depression, delirium, agitation Aggression
Not known	Hallucinations, restlessness, nightmares
Nervous system disorders	
Common Uncommon	Headache, syncope, dizziness Psychomotor hyperactivity
Very rare	Extrapyramidal symptoms
Not known	Worsening of Parkinson's disease, seizure, tremor, somnolence
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 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, 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 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).

Symptoms and Treatment of Overdose:

Symptoms:

Most cases of accidental overdosage 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, diarrhoea, abdominal pain, dizziness, tremor, headache, somnolence, bradycardia, confusional state, hyperhidrosis, hypertension, hallucinations and malaise. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, and convulsions. Muscle weakness is a possibility and may result in death if respiratory muscles are involved. Due to the known vagotonic effect of cholinesterase inhibitors on heart rate, bradycardia and/or syncope may also occur.

Fatal outcome has been rarely reported with rivastigmine overdose and the relationship to rivastigmine was unclear. Symptoms of overdose and outcome vary from patient to patient and the severity of the outcome is not predictably related to the amount of the overdose.

Treatment:
As rivastigmine has a plasma half-life of about 3.4 hours and duration of acetylcholinesterase inhibition of about 9 hours, it is recommended that in cases of asymptomatic overdose all rivastigmine patches should be immediately removed and no further 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 events should be given as necessary.
- In massive overdose, atropine can be used. An initial dose of 0.03 mg/kg i.v. atropine sulfate is recommended, with subsequent doses based on clinical response. Use of scopolamine as an antidote is not recommended.

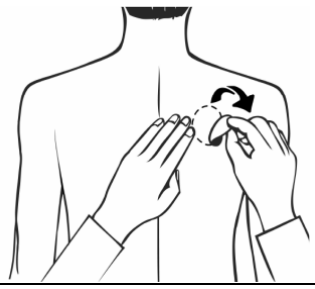
Storage:
Store at below 30 °C.
Keep out of reach of Children.
Jauhi dari kanak-kanak.

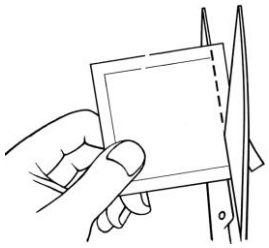
Keep pack in sachet until use

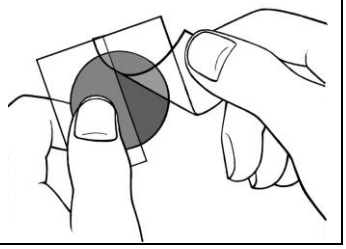
Packing unit:

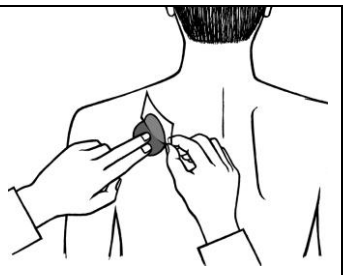
30 Patches

Instructions for Use:

Carefully remove the existing patch before putting on a new one. For patients starting treatment for the first time and for patients restarting Rivacure after treatment interruption, please begin with the second picture.	

Each patch is sealed in its own protective sachet. You should only open the sachet when you are ready to apply the patch. Cut the sachet along the dotted line with scissors and remove the patch from the sachet.	

A protective liner covers the sticky side of the patch. Peel off one side 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 side 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.

Manufacturer:
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