Pendaftar.

NOVARTIS

EXELON® Patch

(rivastigmine)

Transdermal patch 4.6mg/24 hours (Exelon® Patch 5)

Transdermal patch 9.5mg/24 hours (Exelon® Patch 10)

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PERUBAHAN : Sistem no. Bets.

PARAF /TGL : 13-3-18

Leaflet

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Kategori : VaMinor

Perubahan/Penambahan:

- Administratif;
- Indikasi, posologi;
- Informasi produk;
- Penandaan: pabrik produsen ...
- Mutu

Paraf/Tgl: /1.3.17

Trade Name

Exelon® Patch

Description and Composition

Pharmaceutical forms

Transdermal patch.

Each patch is a thin, matrix-type transdermal patch consisting of three layers.

The outside of the backing layer is beige and labelled for each patch dose as follows:

- with "Exelon® Patch 5" and "AMCX"
- with "Exelon® Patch 10" and "BHDI"

Active substance

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

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

Excipients

Vitamin E, poly butylmethacrylate, methyl-methacrylate, acrylic copolymer, silicone oil (Ph. Eur.).

Indications

Symptomatic treatment of mild to moderately severe Alzheimer's dementia

Treatment of patients with mild to moderately severe dementia associated with Parkinson's disease.

Dosage & Administration

Posology

Patches	Rivastigmine base dose load	Rivastigmine base *in vivo* release rates per 24 h
Exelon Patch 5	9 mg	4.6 mg
Exelon Patch 10	18 mg	9.5 mg

Perubahan/Penambahan:
- Administrasi;
- Indikasi posologi;
- Informasi produk;
- Penandaan

Paraf/Tgl: 1.3.17

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Special population

(See section warnings and precautions)

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 Warnings and precautions and Clinical pharmacology – Pharmacokinetics.

Renal impairment

No dose adjustment is necessary for patients with renal impairment (see section Clinical pharmacology - Pharmacokinetics).

Pediatric patients

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

Contraindications

The use of Exelon is contraindicated in patients with:

- known hypersensitivity to rivastigmine, to other carbamate derivatives or to the excipients of the formulation (see section Description and composition - Excipients)
- previous history of application site reactions suggestive of allergic contact dermatitis with rivastigmine transdermal patch (see section Warnings and precautions – Skin reactions)

Warnings and Precautions

Misuse of the medicinal product and dosing errors resulting in overdose

Misuse of the medicinal product and dosing errors with Exelon transdermal patch have resulted in serious adverse reactions; some cases have required hospitalization, and rarely led to death (see section Overdosage). 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 Exelon transdermal patch (see section Dosage and administration).

Gastrointestinal disorders

The incidence and severity of adverse events generally increase with increasing doses, particularly at dose changes. If treatment is interrupted for more than several days, it should be re-initiated with Exelon Patch 5.

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Gastrointestinal disorders such as nausea and vomiting may occur when initiating treatment and/or increasing the dose. They may respond to a dose reduction. In other cases, use of Exelon patches has been discontinued. Patients who show signs or symptoms of dehydration resulting from prolonged vomiting or diarrhoea can be managed with iv fluids and dose reduction or discontinuation if recognized and treated promptly. Dehydration can be associated with serious outcomes (see section Adverse drug Reactions).

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 Exelon patches.

Other adverse reactions from increased cholinergic activity

As with other cholinergic substances care must be taken when prescribing Exelon patches:

- to patients with sick sinus syndrome or conduction defects (sino-atrial block, atrio-ventricular block) (see section Adverse drug Reactions).
- to patients with active gastric or duodenal ulcers or patients predisposed to these conditions because gastric acid secretions may be increased.
- 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.

Like other cholinomimetics, rivastigmine may induce or exacerbate extrapyramidal symptoms. In patients with dementia associated with Parkinson's disease who were treated with Exelon capsules, worsening of parkinsonian symptoms, particularly tremor, has been observed.

Skin reactions

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

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, edema, papules, vesicles) and if symptoms do not significantly improve within 48 hours after patch removal. In these cases, treatment should be discontinued (see section Contraindications).

There have been isolated 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 Contraindications). Patients and caregivers should be instructed accordingly.

Other warnings and precautions

Rivastigmine may exacerbate or induce extrapyramidal symptoms.

Contact with the eyes should be avoided after handling Exelon transdermal patches (see section Non-clinical safety data). Hands should be washed with soap and water after removing the patch. In case contact with eyes or if the eyes become red after handling the patch, rince 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 events and may be more likely to discontinue due to adverse events. Particular caution should be exercised in titrating these patients above the recommended maintenance dose of Exelon Patch 10.
- Hepatic impairment: Patients with clinically significant hepatic impairment may experience more adverse reactions. Dosing recommendations to titrate according to individual tolerability should be closely followed. Patients with severe hepatic impairment have not been studied. Particular caution should be exercised in titrating these patients (see section Dosage and administration and section Clinical pharmacology - Pharmacokinetics).

Driving and using machines

Alzheimer's and Parkinson's disease dementia may cause gradual impairment of driving performance or compromise the ability to use machinery. Rivastigmine may induce dizziness and somnolence, mainly when initiating treatment or increasing the dose. 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.

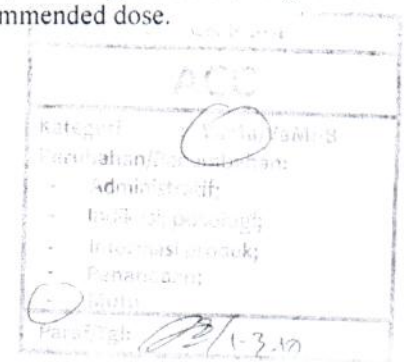
Adverse Drug Reactions

The overall incidence of adverse events in patients treated with Exelon Patch 10 was lower than the rate in patients who received Exelon capsule treatment. Gastrointestinal adverse events, including nausea and vomiting were the most common adverse events in patients who received active treatment, and occurred at substantially lower rate in the Exelon Patch 10 group compared to the Exelon capsule group (7.2% vs 23.1% for nausea and 6.2% vs 17.0% for vomiting; 5.0% and 3.3% of patients on placebo reported nausea and vomiting, respectively).

The most commonly reported adverse drug reactions are gastrointestinal including nausea and vomiting, especially during titration.

Adverse reactions in table-1 and table-2 are ranked under headings of frequency, the most frequent first, using the following convention: 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), including isolated reports.

Significant gastrointestinal adverse reaction including nausea, vomiting, anorexia, weight loss have been reported with the Exelon patch at higher than recommended dose.



The following adverse drug reactions were reported in patients with Alzheimer's dementia treated with Exelon Patch.

Table 1 Adverse drug reactions reported in 2687 patients with Alzheimer's dementia treated for 24 weeks to 48 weeks in randomized controlled clinical studies with Exelon patches at all doses (Exelon Patch 5 to Exelon Patch 10).

Metabolism and nutrition disorders	
Common	Anorexia, decreased appetite
Uncommon	Dehydration
Psychiatric disorders	
Common	Anxiety, depression, insomnia
Uncommon	Agitation, delirium, hallucinations, aggression
Nervous system disorders	
Common:	Dizziness, headache
Uncommon:	Cerebrovascular accident, syncope, somnolence*, psychomotor hyperactivity
Very rare	Extrapyramidal symptoms
Cardiac disorders	
Uncommon:	Cardiac arrhythmia (e.g bradycardia, supraventricular extrasystole)
Gastrointestinal disorders	
Very common	Nausea
Common:	Vomiting, diarrhoea, dyspepsia, abdominal pain
Uncommon:	Gastric ulcer, gastrointestinal haemorrhage (e.g hemorrhagic duodenitis)
Renal and urinary disorders	
Common	Urinary incontinence
Skin and subcutaneous tissue disorders	
Common:	Rash
Uncommon	Hyperhidrosis
General disorders and administration site conditions	
Common:	Application site reactions, application site erythema**, application site pruritus**, application site oedema**, fatigue, asthenia, application site irritation, pyrexia,
Uncommon	Contact dermatitis**, malaise
Rare	Fall
Investigations	
Common	Weight decrease
Infections and infestations	
Common	Urinary tract infection

*In a 24 week controlled study in Chinese patients somnolence was reported as "common".

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

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Table-2 Adverse drug reactions reported in 24-week period in the open-label clinical study conducted with Exelon transdermal patches in patients with dementia associated with Parkinson's disease

Adverse drug reactions		Exelon Patch n (%)
Total patients studied		288 (100)
Psychiatric disorders		
Common:	Insomnia	18 (6.3)
Common:	Depression	16 (5.6)
Common:	Anxiety	15 (5.2)
Common:	Agitation	8 (2.8)
Nervous system disorders		
Common:	Tremor	21 (7.3)
Common:	Dizziness	16 (5.6)
Common:	Somnolence	12 (4.2)
Common:	Hypokinesia	11 (3.8)
Common:	Bradykinesia	10 (3.5)
Common:	Cogwheel rigidity	8 (2.8)
Common:	Dyskinesia	7 (2.4)
Gastrointestinal disorders		
Common:	Abdominal pain	6 (2.1)
Vascular disorders		
Common:	Hypertension	9 (3.1)
General disorders and administration site conditions		
Very Common:	Fall	34 (11.8)
Very Common:	Application site erythema	31 (10.8)
Common:	Application site irritation, pruritus, rash	9 (3.1); 13 (4.5); 7 (2.4)
Common:	Fatigue	10 (3.5)
Common:	Asthenia	6 (2.1)
Common:	Gait disturbance	11 (3.8)

Additional adverse reactions observed during a 76-week prospective, open-label study in patients with dementia associated with Parkinson's disease treated with Exelon transdermal patches: dehydration, weight decreased, aggression, hallucination visual (common).

In patients with dementia associated with Parkinson's disease the following adverse drug reactions have only been observed in clinical trials with Exelon capsules: nausea, vomiting (very common); decreased appetite, restlessness, worsening of Parkinson's disease, bradycardia, diarrhoea, dyspepsia, salivary hypersecretion, sweating increased (common); dystonia, atrial fibrillation, atrioventricular block (uncommon).

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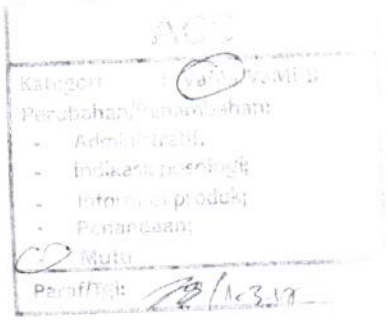


Adverse drug reactions from post-marketing spontaneous reports

The following additional adverse drug reactions have been identified based on post-marketing spontaneous reports. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Rarely reported: hypertension, application site hypersensitivity, pruritus, rash, erythema, urticaria, blister, dermatitis allergic.

Very rarely reported: tachycardia, atrioventricular block, atrial fibrillation, pancreatitis, fall, seizure. Parkinson's disease (worsening) has been observed in patients with Parkinson's disease who were treated with Exelon patches.

Frequency not known: dehydration, hepatitis, aggression, restlessness, and sick sinus syndrome, abnormal liver function tests, allergic dermatitis (disseminated), extrapyramidal symptoms in patients with Alzheimer's dementia, tremor, nightmares.

Additional adverse drug reactions which have been reported with Exelon capsules

Very rare: Urinary tract infections, cardiac arrhythmia (e.g. atrio-ventricular block atrial, fibrillation and tachycardia), hypertension, pancreatitis, gastrointestinal haemorrhage, hallucination; and some cases of severe vomiting were associated with oesophageal rupture.

Rare: seizures, duodenal ulcers, angina pectoris, myocardial infarction

Uncommon: insomnia, fall

Common: agitation, somnolence, malaise, tremor, confusion, hyperhidrosis

Very common: dizziness, loss of appetite

Information from clinical trials in patient with Alzheimer's dementia treated with Exelon patches

The following adverse events were reported in patient with Alzheimer's dementia treated with Exelon patches.

Table-3: Adverse events (≥2% in all Exelon Patch groups) from the specific 24-week double-blind placebo controlled clinical trial conducted with Exelon patches in patients with Alzheimer's dementia

	Exelon Patch 10 group n (%)	Exelon Patch 20 group n (%)	Exelon capsules 12 mg/day n (%)	Placebo n (%)	All Exelon patches group n (%)
Total patients studied	291	303	294	302	594
Total patients with AE(s)	147 (50.5)	200 (66.0)	186 (63.3)	139 (46.0)	347(58.4)
Nausea	21 (7.2)	64 (21.1)	68 (23.1)	15 (5.0)	85(14.3)
Vomiting	18 (6.2)	57 (18.8)	50 (17.0)	10 (3.3)	75(12.6)

Diarrhoea	18 (6.2)	31 (10.2)	16 (5.4)	10 (3.3)	49(8.2)
Weight decreased	8 (2.7)	23 (7.6)	16 (5.4)	4 (1.3)	31(5.2)
Dizziness	7 (2.4)	21 (6.9)	22 (7.5)	7 (2.3)	28(4.7)
Decreased appetite	2 (0.7)	15 (5.0)	12 (4.1)	3 (1.0)	17(2.9)
Headache	10 (3.4)	13 (4.3)	18 (6.1)	5 (1.7)	23(3.9)
Anorexia	7 (2.4)	12 (4.0)	14 (4.8)	3 (1.0)	19(3.2)
Depression	11 (3.8)	12 (4.0)	13 (4.4)	4 (1.3)	23(3.9)
Insomnia	4 (1.4)	12 (4.0)	6 (2.0)	6 (2.0)	16(2.7)
Abdominal pain	7 (2.4)	11 (3.6)	4 (1.4)	2 (0.7)	18(3.0)
Asthenia	5 (1.7)	9 (3.0)	17 (5.8)	3 (1.0)	14(2.4)
Anxiety	9 (3.1)	8 (2.6)	5 (1.7)	4 (1.3)	17(2.9)
Fatigue	5 (1.7)	7 (2.3)	2 (0.7)	4 (1.3)	12(2.0)

Skin irritation

Skin irritation, when observed, was mostly slight or mild in severity and was rated as severe in ≤2.2% of Exelon Patch patients, versus ≤1.0% of placebo patch patients.

Interactions

No specific interaction studies have been conducted with Exelon 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.

Anticipated interactions resulting in a concomitant use not recommended

Metoclopramide

Considering the possibility of an additive extra-pyramidal effect the concomitant use of metoclopramide and rivastigmine is not recommended.

Drugs acting on cholinergic system

In view of its pharmacodynamic effects, rivastigmine should not be given concomitantly with other cholinomimetic drugs due to possible additive effect. Rivastigmine might also interfere with the activity of anticholinergic medications (e.g. oxybutynin, tolterodine).

Succinylcholine-type muscle relaxants

As a cholinesterase inhibitor, rivastigmine may exaggerate the effects of succinylcholine-type muscle relaxants during anaesthesia.

Observed interactions to be considered

Beta-blockers

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. Cardioselective beta-blockers are expected to be associated with the greatest risk, but reports have also been received in patients using other beta-blockers.

Interaction with nicotine

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

Interactions with commonly used concomitant drugs

No pharmacokinetic interaction was observed between 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 rivastigmine. No untoward effects on cardiac conduction were observed following concomitant administration of digoxin and rivastigmine.

Concomitant administration of rivastigmine with commonly prescribed medications, such as antacids, antiemetics, antidiabetics, centrally acting antihypertensives, β-blockers, calcium channel blockers, inotropic drugs, antianginals, non-steroidal anti-inflammatory drugs, 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.

Women of child-bearing potential, pregnancy, breast-feeding and fertility

Women of child-bearing potential

There is no information available on the effects of rivastigmine in women of child-bearing potential.

Pregnancy

In pregnant animals, rivastigmine and/or metabolites crossed the placenta. It is not known if this occurs in humans. In animal studies, rivastigmine was not teratogenic. However, the safety of Exelon in human pregnancy has not been established, and it should only be given to pregnant women if the potential benefit outweighs the potential risk for the foetus.

Breast-feeding

In animals, rivastigmine and/or metabolites were excreted in breast milk. It is not known if Exelon is excreted into human milk, and patients on Exelon should therefore not breast-feed.

Fertility

In 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 (see section Non-clinical safety data). There is no information available on the effects of rivastigmine on human fertility.

Overdosage

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.

Overdose with Exelon patches resulting from misuse/medication errors (application of multiple patches at a time) has been reported in the post-marketing setting and rarely in clinical trials. Fatal outcome has been rarely reported with rivastigmine overdose and relationship to rivastigmine was unclear. Symptoms of overdose and outcome vary from patient to patient, nor is the severity of the outcome predictably related to amount of the overdose.

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 Exelon 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.

Clinical Pharmacology

Mechanism of action/ Pharmacodynamic properties (PD)

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, Exelon 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. In healthy young men, an oral 3.0 mg dose decreases acetylcholinesterase (AChE) activity in cerebro spinal fluid (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. Butyrylcholinesterase (BuChE) activity in CSF was transiently inhibited and was no longer different from baseline after 3.6 hours in healthy young volunteers. In patients with Alzheimer's Disease (AD), inhibition of acetylcholinesterase in CSF by rivastigmine was dose-dependent up to 6 mg given twice daily, the highest dose tested. Inhibition of BuChE activity in CSF of AD patients by rivastigmine was similar to that of AchE, with a change from baseline of more than 60% after 6 mg given twice daily. The effect of rivastigmine on AChE and BuChE activity in CSF was sustained after 12 months administration, the longest time studied. Statistically significant correlations were found between the degree of inhibition by rivastigmine of AChE and BuChE in the CSF and changes on a compound measure of cognitive performance in AD patients; however, only BuChE inhibition in CSF was significantly and consistently correlated with improvements in speed-, attention- and memory-related subtests.

Pharmacokinetic Properties

Absorption

Absorption of rivastigmine from Exelon patches is slow. After the first dose, detectable plasma concentrations are observed after a lag time of 0.5-1 hour. Concentrations then rise slowly and typically after 8 hours reach levels close to maximum, although maximum values (C_{max}) are often reached at later times (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 patch is replaced with a new one, plasma concentrations initially decrease slowly for about 40 min on average, until absorption from

the newly applied patch becomes faster than the 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 dosing, with which concentrations fall off to virtually zero between doses (see Figure 1). This time course of plasma concentrations is observed with all patch strengths (sizes) in the investigated range. Although less pronounced than with the oral formulation, exposure to rivastigmine (C_{max} and AUC) increased over-proportionally with rising patch doses. Escalating from Exelon Patch 5 to Exelon Patch 10, the increase in rivastigmine AUC was 2.6 fold. The fluctuation index (FI), i.e. a measure of the relative difference between peak and trough concentrations ($(C_{max}-C_{min})/C_{avg}$), was in the range 0.57 to 0.77 for the patch, thus demonstrating a much smaller fluctuation between trough and peak concentrations than for the oral formulation (FI = 3.96 to 6.24). As determined by compartmental modeling the Exelon Patch 10 exhibited exposure equivalent to that provided by an oral dose of about 6 mg twice daily (i.e. 12 mg/day)

Figure 1 **Rivastigmine plasma concentrations following dermal 24-hour patch application**

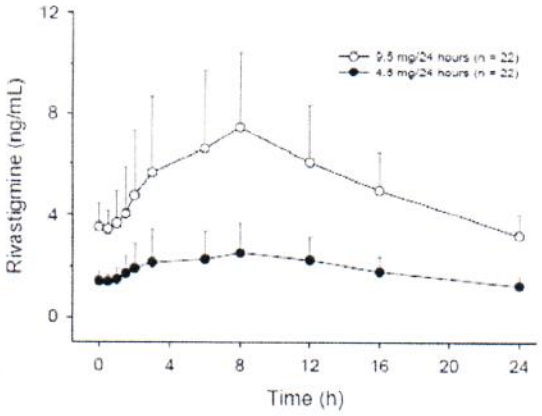
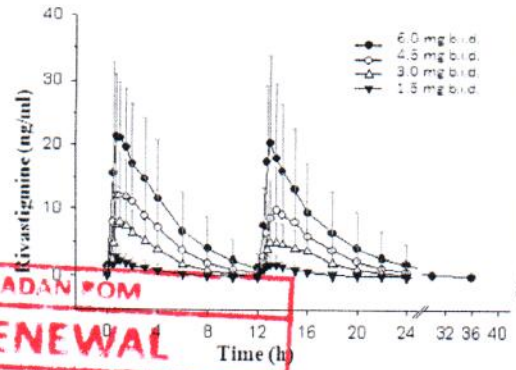


Figure 2 **Rivastigmine plasma concentrations following oral (twice daily) capsule**



In a single dose study directly comparing the patch versus oral administration, the inter-subject variability in rivastigmine pharmacokinetic parameters (normalised to dose/kg bodyweight) was 43% (C_{max}) and 49% (AUC_{0-24h}) after the patch versus 74% and 103%, respectively, after the oral capsule. Similarly, inter-subject variability in rivastigmine pharmacokinetic parameters was lower after the patch than after the oral capsule in a steady-state study in Alzheimer's dementia patients given repeated doses. The inter-patient variability was at most 45% (C_{max}) and 43% (AUC_{0-24h}) after the patch, while 71% and 73%, respectively, after the oral form.

A relationship between drug 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 drug exposure suggests special attention to patients with very low body weight during up-titration (see section Dosage and Administrations).

Rivastigmine was well released from the transdermal system over a 24-hour dermal application with approximately 50% of the drug load released from the system.

Exposure (AUC_∞) to rivastigmine (and metabolite NAP266-90) was highest when the patch was applied to the upper back, chest, or upper arm. Two other sites (abdomen and thigh) could be used if none of the three other sites is available, but the practitioner should keep in mind that the rivastigmine plasma exposure associated with these sites was approximately 20-30% lower.

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

Metabolism

Rivastigmine is rapidly and extensively metabolised with an apparent elimination half-life in plasma of approximately 3.4 hours after patch removal. Elimination was absorption rate limited (flip-flop kinetics), which explains the longer $t_{½}$ after patch (3.4 h) versus oral or i.v. administrations (1.4 to 1.7 h). Metabolism is primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite. In vitro, this metabolite shows minimal inhibition of acetylcholinesterase (<10%). Based on *in vitro* studies, no pharmacokinetic drug interactions are expected with drugs metabolized by the following cytochrome isoenzymes: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, CYP2C19, or CYP2B6. Based on evidence from in vitro and animal studies, the major cytochrome P450 isoenzymes are minimally involved in rivastigmine metabolism. Total plasma clearance of rivastigmine was approximately 130 litres/h after a 0.2 mg intravenous dose and decreased to 70 litres/h after a 2.7 mg intravenous dose, which is consistent with the non-linear, overproportional pharmacokinetics of rivastigmine due to saturation of its elimination.

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

Elimination

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

Elderly subjects

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

Subjects with hepatic impairment

No study was conducted with the Exelon 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 oral dose or multiple 6-mg twice a day oral doses, the mean oral clearance of rivastigmine was approximately 60-65% lower in mild (n=7, Child-Pugh score 5-6) and moderate (n=3, Child-Pugh score 7-9) hepatically impaired patients (n=10, biopsy proven) than in healthy subjects (n=10). These pharmacokinetic changes had no effect on either the incidence or severity of adverse effects (see section Dosage and administration and section Warnings and precautions).

Subjects with renal impairment

No study was conducted with the Exelon 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 dosage adjustment is necessary in patients with renal impairment (see section Dosage and administration).

Clinical studies

Clinical studies in Alzheimer's Dementia

The efficacy of Exelon 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 active comparator study core study.

24-week placebo-controlled studies

Patients involved in a 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 (a performance-based measure of cognition)

and the ADCS-CGIC (a comprehensive global assessment of the patient by the physician incorporating caregiver input), and the ADCS-ADL (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 4.

Table-4: 24-week results for three assessment tools

	Exelon Patch 10	**Exelon** capsule 12 mg/day	**Placebo**
ITT-LOCF population	N = 251	N = 256	N = 282
ADAS-Cog			
	(n=248)	(n=253)	(n=281)
Mean baseline ± SD	27.0 ±10.3	27.9 ± 9.4	28.6 ± 9.9
Mean change at week 24 ± SD	-0.6 ± 6.4	-0.6 ± 6.2	1.0 ± 6.8
p-value versus placebo	0.005*[1]	0.003*[1]	
ADCS-CGIC			
	(n=248)	(n=253)	(n=278)
Mean score ± SD	3.9 ± 1.20	3.9 ± 1.25	4.2 ± 1.26
p-value versus placebo	0.010*[2]	0.009*[2]	
ADCS-ADL			
	(n=247)	(n=254)	(n=281)
Mean baseline ± SD	50.1 ± 16.3	49.3 ± 15.8	49.2 ± 16.0
Mean change at week 24 ± SD	-0.1 ± 9.1	-0.5 ± 9.5	-2.3 ± 9.4
p-value versus placebo	0.013*[1]	0.039*[1]	

* p≤0.05 versus placebo

ITT: Intent-To-Treat; LOCF: Last Observation Carried Forward

[1] Based on ANCOVA with treatment and country as factors and baseline value as a covariate. Negative ADAS-Cog changes indicate improvement. Positive ADCS-ADL changes indicate improvement.

[2] Based on CMH test (van Elteren test) blocking for country. ADCS-CGIC scores <4 indicate improvement.

The results for clinically relevant responders from the 24-week study are provided in Table-5. 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-5: Result for clinically relevant responders from the 24 week placebo controlled study

	Patients with Clinically Significant Response (%)		
	Exelon Patch 10	Exelon capsule 12mg/day	Placebo
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

Dementia associated with Parkinson's disease

Efficacy and safety of rivastigmine in patients with dementia associated with Parkinson's disease have been demonstrated with Exelon capsules but no study has been conducted with Exelon patches.

Modelled pharmacokinetic data from a study conducted with Exelon patches in Alzheimer's disease patients showed that the total daily exposure (AUC) of the Exelon Patch 10 is approximately equivalent to the exposure obtained with a capsule dose of 6 mg twice daily. The 6 mg twice daily capsule dose was the highest dose used in patients with Parkinson's disease dementia.

Non-clinical safety data

Acute toxicity

The estimated oral LD_{50} values in mice were 5.6 mg base/kg (males) and 13.8 mg base/kg (females). The estimated oral LD_{50} values in rats were 8.1 mg base/kg (males) and 13.8 mg base/kg (females).

Repeated dose toxicity

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.

Mutagenicity

Rivastigmine was not mutagenic in *in vitro* tests for gene mutations and primary DNA damage. In tests for chromosomal damage *in vitro*, a small increase in the number of cells carrying chromosomal aberrations occurred at very high concentrations. However, as there was no evidence of clastogenic activity in the more relevant *in vivo* micronucleus test assessing chromosomal damage test, it is most likely that the *in vitro* findings were false positive observations. In addition, the major metabolite NAP226-90 did not induce structural chromosome aberrations in an *in vitro* test indicating that the compound has no genotoxic potential.

Carcinogenicity

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 patches.

Reproductive toxicity

Oral studies in pregnant rats and rabbits with dose levels up to 2.3 mg base/kg/day gave no indication of teratogenic potential on the part of rivastigmine. Similarly, there was no evidence of adverse effects of rivastigmine on fertility, reproductive performance or in utero

or postnatal growth and development in rats at given dose levels up to 1.1 mg base/kg/day (see section Women of child-bearing potential, pregnancy, breast-feeding and fertility). Specific dermal studies in pregnant animals have not been conducted.

Local tolerance

Rivastigmine patches were not phototoxic and considered to be a non-sensitizer. 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 Exelon patches to induce mild erythema in patients. A mild eye/mucosal irritation potential of rivastigmine was identified in a rabbit study (see section Warnings and precautions).

Pharmaceutical information

Incompatibilities

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

Special precautions for storage

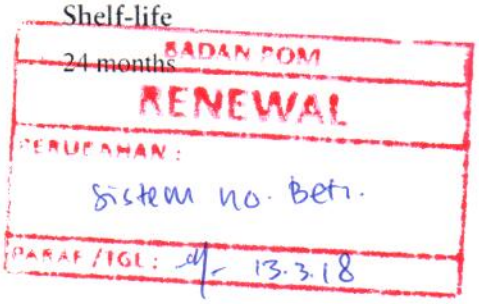
Do not store above 30°C

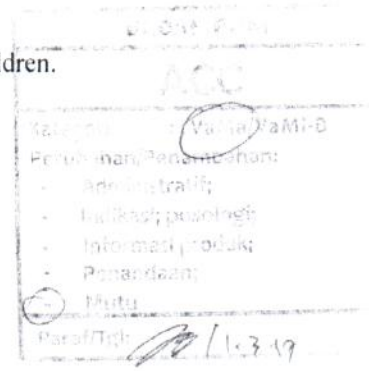
Keep the patch in the sachet until use

Exelon must be kept out of the reach and sight of children.

Shelf-life

24 months

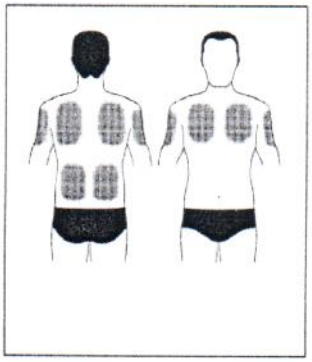




Instruction for use and handling

IMPORTANT: Only one patch should be worn at a time. You must remove the previous day's Exelon Patch **before** applying a new one. Do not cut the patch into pieces.

Where to apply Exelon Patch



- Apply the patch to the upper or lower back, upper arm or chest. Avoid places where the patch can be rubbed off by tight clothing.

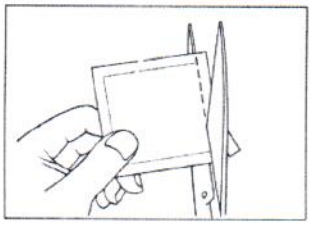
Before you apply Exelon Patch, make sure that your skin is:

- clean, dry and hairless
- free of any powder, oil, moisturiser, or lotion (that could keep the patch from sticking to your skin properly)
- free of cuts, rashes and/or irritations.

When changing your patch, apply your new patch to a different area of skin (for example on the right side of your body one day, then on the left side the next day). Do not apply a new patch to that same area for at least two weeks.

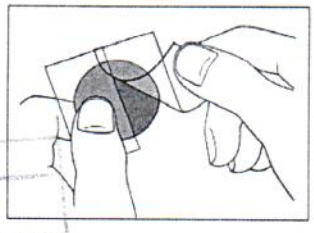
How to apply Exelon Patch

The patch is a thin, opaque, plastic patch that sticks to the skin. Each patch is sealed in a sachet that protects it until you are ready to put it on. Do not open the sachet or remove a patch until just before you apply it.



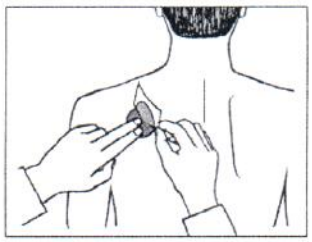
- Each patch is sealed in its own protective sachet. You should only open the sachet when you are ready to apply the patch.

  Cut the sachet along the dotted line or at the notch and remove the patch.

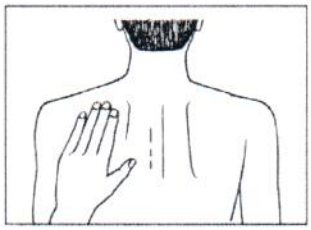


- A protective liner covers the adhesive side of the patch.
  Peel off one side of the protective liner and do not touch the sticky part of the patch with the fingers.

- 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 with the hand to make sure that the edges stick well.



- If it helps you, you may write (e.g. the day of the week) on the Exelon Patch with a thin ball point pen.

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

How to remove Exelon Patch

Gently pull at one edge of the Exelon Patch to remove it completely from the skin.

How to dispose Exelon Patch

After the patch has been removed, fold it in half with the adhesive sides on the inside and press them together. Return the used patch to its original sachet and discard safely out of the reach and sight of children. Wash your hands with soap and water after removing the patch.

Can the patch be worn when bathing, swimming, or in the sun?

- Bathing, swimming, or showering should not affect the patch. When swimming, you can wear the patch under your swimming costume. Make sure the patch does not loosen during these activities.
- The patch should not be exposed to any external heat sources (excessive sunlight, saunas, solarium) for long periods of time.

What to do if Exelon Patch falls off

If the patch falls off, a new patch should be applied for the rest of the day, then replace the patch the next day at the same time as usual.

Note: Exelon Patch should be kept out of the reach and sight of children.

Instruction for disposal

Used patches should be folded, with the adhesives surfaces pressed together, and discarded safely and out of reach and sight of children.

HARUS DENGAN RESEP DOKTER

Package Quantities and Registration Number

Exelon® Patch 5 : Box @ 30 sachets; Reg No.: DKI0867507255A1

Exelon® Patch 10: Box @ 30 sachets; Reg No.: DKI0867507255B1

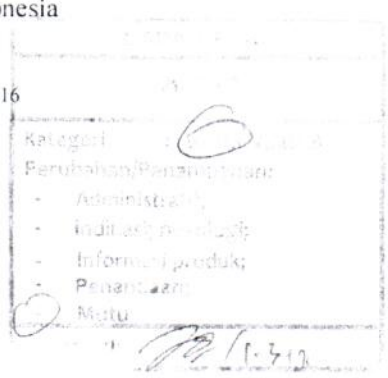
Manufactured by LTS Lohmann Therapie-Systeme, Germany for Novartis Pharma AG, Basel, Switzerland.

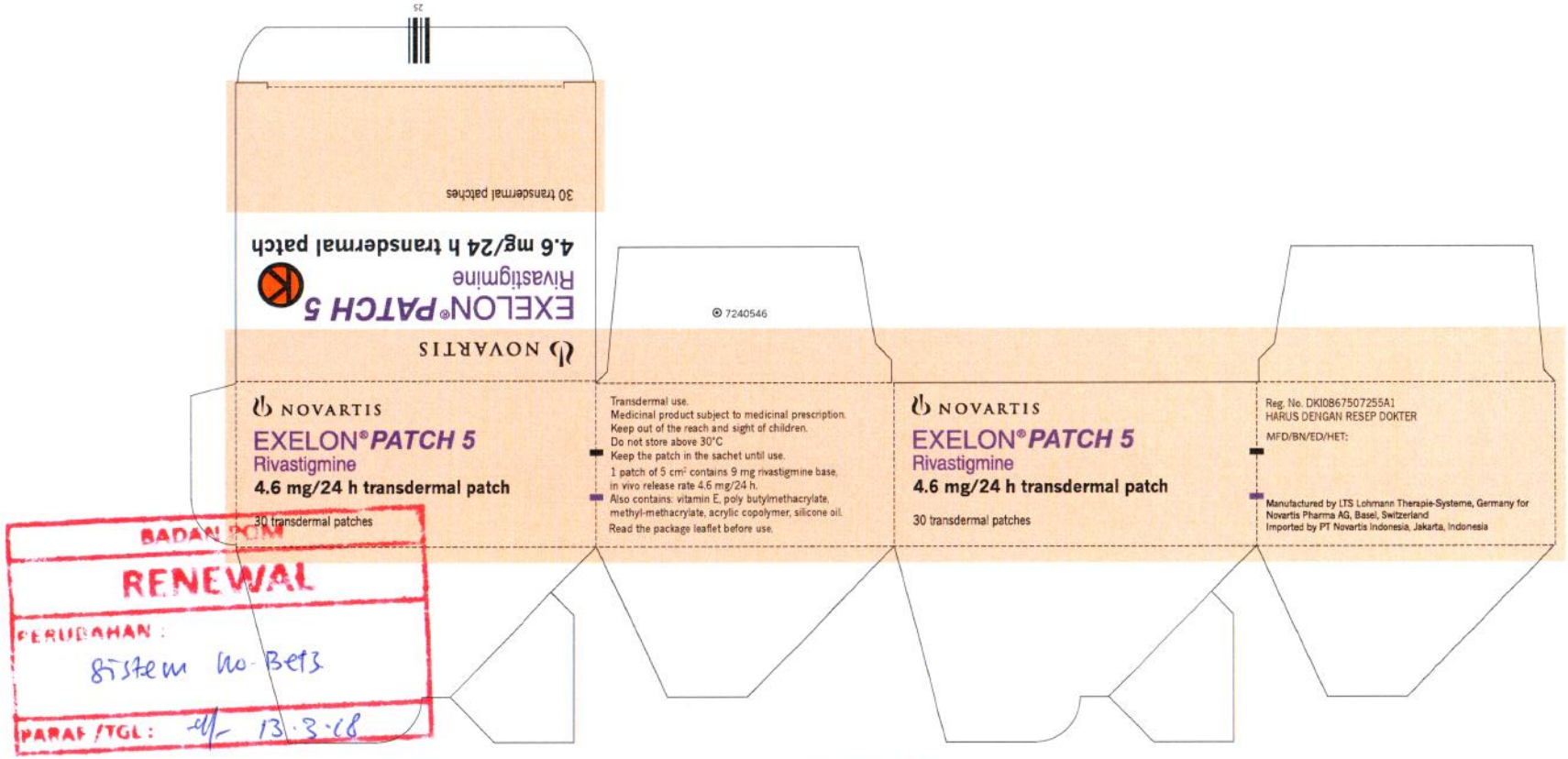
Imported by PT Novartis Indonesia, Jakarta, Indonesia

Update leaflet version based on CDS 28-May-2014 and 4-Mar-2016

(new proposed leaflet for change in storage condition)

BADAN POM
RENEWAL
PERUBAHAN :
sistem no. Bets.
PARAF /TGL : 13-3-18





BADAN POM
RENEWAL
PERUBAHAN : Sistem No Batch
PARAF /TGL : 13-3-18

SIRKULASI

NOVARTIS — PACKAGING DEVELOPMENT, Supply Chain Management Dept.

Code No:	Proof ke :	Description packaging material :
7240546	1	PC EXELON TTS 9MG/5CM2 (JS) V01

Colour : P BLACK C, P 668 C, P 475 C, P WARM RED

No AW : 110/2017

pharmacode: 25

Size : 66 X 36 X 80 mm

Material : Ivory 270 g/m2

Prepared by Pack Dev:	DRA: OK/Not ok	QA: OK/Not ok	Marketing: OK/Not ok	Production: (Local/Third party) OK/Not ok
Sign / Date	Sign / Date	Sign / Date	Sign / Date	Sign / Date
Comment:	Comment:	Comment:	Comment:	Comment:

Note / Correction : According to CR TW 829196

NOVARTIS

EXELON® *PATCH 5*

RIVASTIGMINE

4.6 mg/24 h

transdermal patch

Transdermal use. Keep out of the reach and sight of children. Do not store above 30°C. Keep patch in the sachet until use. Medicinal product subject to medical prescription. Read the package leaflet before use.

EXP

LOT

MFD

BADAN POM

RENEWAL

PERUBAHAN :

Sistem no. Bets

PARAF /TGL : 13.3.18

NOVARTIS

EXELON® *PATCH 5*

RIVASTIGMINE

4.6 mg/24 h

transdermal patch

Reg. No. DKI0867507255A1

HARUS DENGAN RESEP DOKTER

HET :

Manufactured by LTS Lohmann Therapie-Systeme, Germany for Novartis Pharma AG, Basel, Switzerland

Imported by PT Novartis Indonesia, Jakarta, Indonesia

FOR REGISTRATION ONLY

NOVARTIS

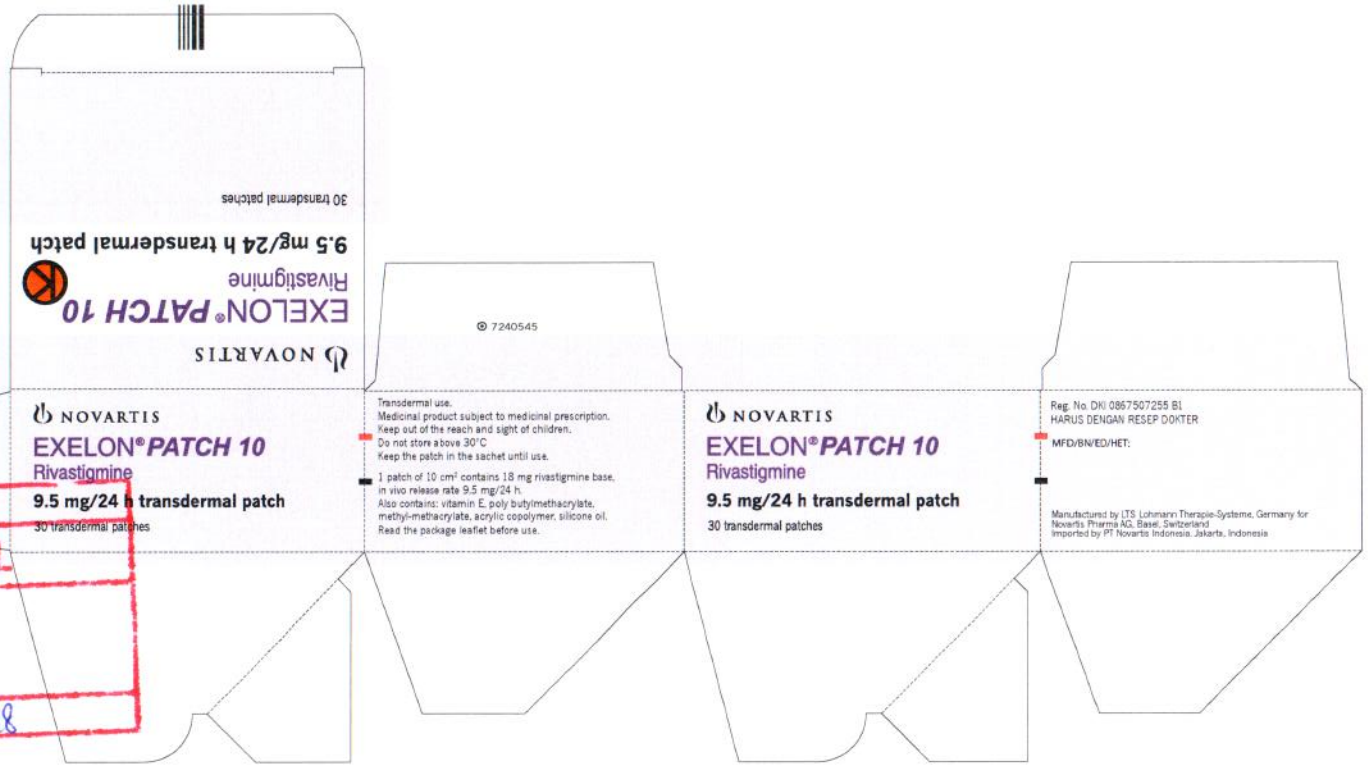
PACKAGING DEVELOPMENT

Supply Chain Management Dept.

Lailasari Halimah

Kurniawan Firdaus Candra

Code No: NA	**Proof ke :** 1	**Description packaging material :** **St patch Exelon 5**
Colour : P BLACK P 475 P 668 P WARM RED		**No AW :** N/099/2016
Size (width x length x height) : 76 x 76 mm		**Material :** pouch
Note / Correction :: Brand name: News Gothic Bold (12pt) Generic name: News Gothic Bold (9,6pt)		



BADAN POM
RENEWAL
PERUBAHAN :
Sistem no. Bets
PARAF /TGL : 13.3.18

SIRKULASI

NOVARTIS			PACKAGING DEVELOPMENT Supply Chain Management Dept.	
Code No: 7240545	**Proof ke :** 1	**Description packaging material :** PC EXELON TTS 18MG/10CM2 (IS) V01		
Colour : P BLACK C, P 668 C, P 663 C, P WARM RED			**No AW :** 111/2017 **Pharmacode:** 55	
Size : 80 X 72 X 36 mm			**Material :** Ivory 270 gsm	
Prepared by Pack Dev: Sign / Date Comment:	**DRA: OK/Not ok** Sign / Date Comment:	**QA: OK/Not ok** Sign / Date Comment:	**Marketing: OK/Not ok** Sign / Date Comment:	**Production: (Local/Third party) OK/Not ok** Sign / Date Comment:
Note / Correction : According to CR TW 829196				

NOVARTIS

EXELON® *PATCH 10*
RIVASTIGMINE
9.5 mg/24 h
transdermal patch

Transdermal use. Keep out of the reach and sight of children. Do not store above 30°C. Keep patch in the sachet until use. Medicinal product subject to medical prescription. Read the package leaflet before use.

EXP
LOT
MFD

BADAN POM
RENEWAL
PERUBAHAN : Sistem no. Bets
PARAF /TGL : 13-3-18

NOVARTIS

EXELON® *PATCH 10*
RIVASTIGMINE
9.5 mg/24 h
transdermal patch

Reg. No. DKI 0867507255 B1
HARUS DENGAN RESEP DOKTER

Manufactured by LTS Lohmann Therapie-Systeme, Germany for Novartis Pharma AG, Basel, Switzerland
Imported by PT Novartis Indonesia, Jakarta, Indonesia

FOR REGISTRATION ONLY

NOVARTIS		***PACKAGING DEVELOPMENT*** Supply Chain Management Dept.
Code No: NA	**Proof ke :** 1	**Description packaging material :** **St patch Exelon 10**
Colour : P BLACK P 663 P 668 P WARM RED		**No AW :** N/100/ 2016
Size (width x length x height) : 76 x 76 mm		**Material :** pouch
Note / Correction : Brand name: News Gothic Bold (12pt) Generic name: News Gothic Bold (9,6pt)		

Lailasari Halimah

Kumiawan Firdaus Candra