Zeyzelf®

twice weekly rivastigmine transdermal patch

Zeyzelf® rivastigmine twice weekly transdermal patch

Offer your mild to moderately severe Alzheimer's dementia patients established efficacy with the convenience of twice weekly application.[1–9]

Zeyzelf® is indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia.[1]

Prescribing Information and Adverse Event Reporting can be found on page 21.

For further information please visit:
www.luye.co.uk

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Luye Pharma

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Zeyzelf®

Overview

Zeyzelf® rivastigmine – *the only* twice weekly transdermal patch in the UK, developed by Luye Pharma, for the treatment of Alzheimer's dementia (AD)[1]

Available in 4.6 mg/24 h and 9.5 mg/24 h dose strengths.[1]

Zeyzelf® is a translucent polymer matrix patch designed to allow release of rivastigmine for up to 4 days, including an adhesive cover to optimise adhesion.[1]

Zeyzelf® adhesive cover

Transdermal delivery in Alzheimer's dementia

Transdermal administration of rivastigmine facilitates access to high-dose efficacy without compromising tolerability[2,4]

Rivastigmine is the only acetylcholinesterase (AChE) inhibitor that is available in a transdermal formulation in the UK.

The 9.5 mg/24 h twice weekly patch **provides efficacy similar to the highest recommended daily dose of oral rivastigmine** (6 mg bid) with improvements in dementia symptoms including:[2,3]

- Cognition
- Global performance
- Attention
- Activities of daily living

Transdermal patches offer **superior tolerability** vs orally administered rivastigmine.[2]*

Fewer patients reported nausea (7.2% vs 23.1%) and vomiting (6.2% vs 17%) on transdermal patches compared with oral rivastigmine.[2]

Transdermal administration delivers reduction in certain side effects vs oral rivastigmine due to:[2,10]

- **Avoiding the first pass effects**[10]
- **Lowered maximum plasma concentration (C_{max})** and **prolonged time to reach C_{max} (T_{max})** for the same exposure[2]
- **Reduced fluctuations** of plasma drug levels and **continuous delivery**[2,10]

If adverse events occur, drug delivery can be promptly ceased by simple patch removal.[10]

In addition to lower risk of side effects, transdermal route of administration can provide greater adherence to the treatment regimen and has less risk of dose dumping compared with the oral route. This is especially important because of increased need of medication in older patients who may need concomitant treatment for multiple chronic conditions.[11]

*Data from a study comparing 9.5 mg/24 h daily patch (n=229) vs 12 mg/day oral rivastigmine (n=266).[2]

Zeyzelf®

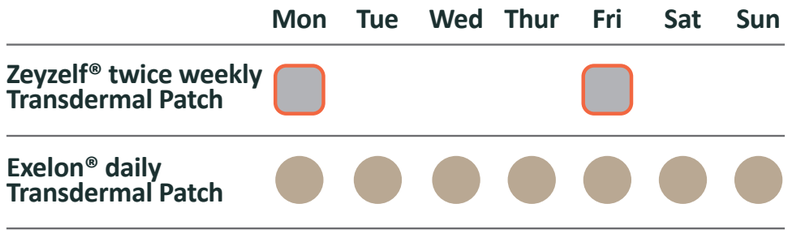
Convenient, twice weekly administration[1]

Helping to simplify the lives of patients as well as their caregivers with:

- Reduced pill burden for patients with multimorbidity
- Suitable for patients who have trouble with, or are unable or unwilling to swallow pills or difficulty in swallowing, in general - a trait closely related to frailty in patients with mild to moderate Alzheimer's disease[12]
- Reduced caregiver burden
- Visual indicator of compliance

With the ease of fixed day twice weekly dosing, carers can more easily plan the dosing schedule to the patient's and their own convenience.

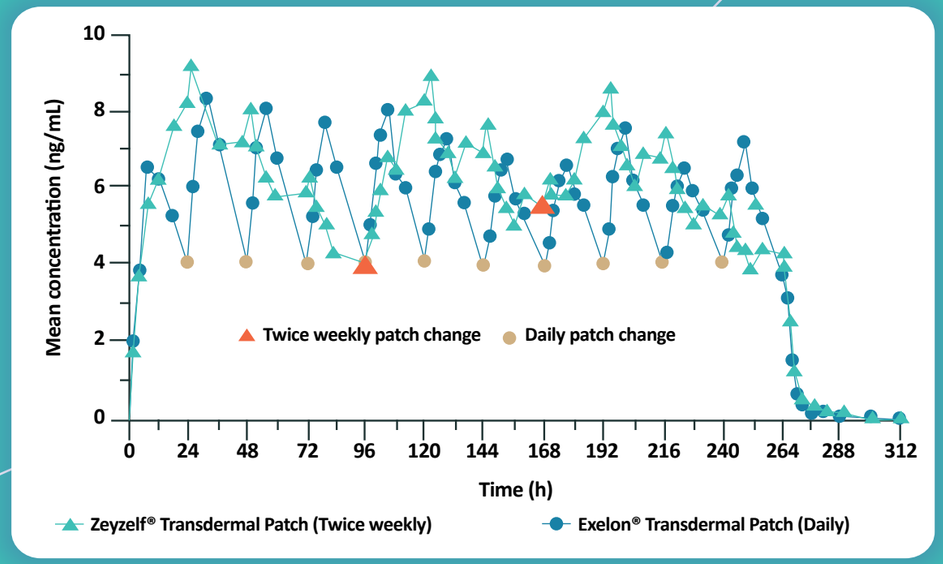
Schematic representation of patch application



Example of a dosing schedule. Twice weekly patches should be applied on fixed days, at an interval of 4 and 3 days, respectively.[1]

Rivastigmine twice weekly transdermal patch

Zeyzelf® twice weekly is bioequivalent to the originator Exelon® daily transdermal patch[3]



Graph adapted from Schurad B, et al.[3]

Rivastigmine mean plasma concentrations over time.

Zeyzelf® is the only transdermal rivastigmine patch with twice weekly application.

Less frequent application vs a daily patch gives **the option of dosing (application) free days** for the carer and patients, e.g., weekends could be dosing (application) free if the patches are applied on Mondays and Fridays.

Establishing fixed days of application will help the patient and caregiver to maintain a routine and adherence to the medication.[3]

Zeyzelf®

Zeyzelf® transdermal patches come with adhesive covers to apply over the patch, providing additional security with peace of mind for the patients and their caregivers

Zeyzelf® patch and adhesive cover

Active patch

Images not to scale, but proportionate.

Adhesive cover

To optimise adhesion to the skin a separate oval shaped adhesive cover is provided which is applied over the active patch.

The active transdermal patch is thin and rectangular in shape.

The patch cover can be written on, giving carers an opportunity to record details like the date and time of application and/or for the patch change.

A study comparing the twice weekly Zeyzelf® patch and Exelon® daily patch showed Zeyzelf® had better adhesion properties despite the longer dosing intervals.[3]

Percentage of assessments showing ≥90% adhesion for Zeyzelf® compared to <70% for Exelon®[3]

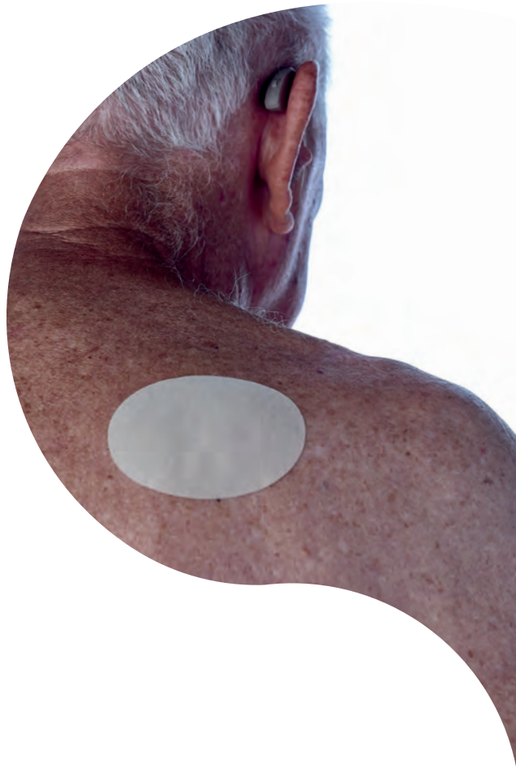
Significance not reported

Zeyzelf® twice weekly patch	94.83%
Exelon® daily patch	66.77%

Figure based on data from Schurad B, et al.[3]

The EMA Guideline defines satisfactory adhesion as ≥ 90% of area that remained adhered at assessment. Assessments were done at 24 h post application of the patches.[14]

Poor adhesion may lead to improper dosing, increased usage of patches, and additional caregiver and healthcare professional time.[13]



Rivastigmine therapy in Alzheimer's dementia

Efficacy

Use of Zeyzelf® early on in Alzheimer's patients can offer robust efficacy and help delay progression.[5]

Rivastigmine may improve activities of daily living, particularly in patients who already have functional impairment.[15]

Efficacy of rivastigmine and donepezil in patients receiving treatment for 2 years (ITT-LOCF)[9]

Patients treated with rivastigmine had significant favourable differences with this treatment in the maintenance of activities of daily living (ADCS-ADL) and global functionality (GDS) compared with donepezil (ITT-LOCF) at two years.[9]

Efficacy measure	Rivastigmine		Donepezil		p-value
	n	LS mean change from baseline at Week 104	n	LS mean change from baseline at Week 104	
GDS	471	0.58 (0.9)*	483	0.69 (0.9)*	0.049**
ADCS-ADL	454	-12.79 (0.9)	475	-14.87 (0.9)	0.047†

Adapted from Bullock M, et al. 2005.[9]

*Mean with SE.
** p-value calculated using the Wilcoxon rank-sum test.
†p-value calculated using the ANCOVA model.

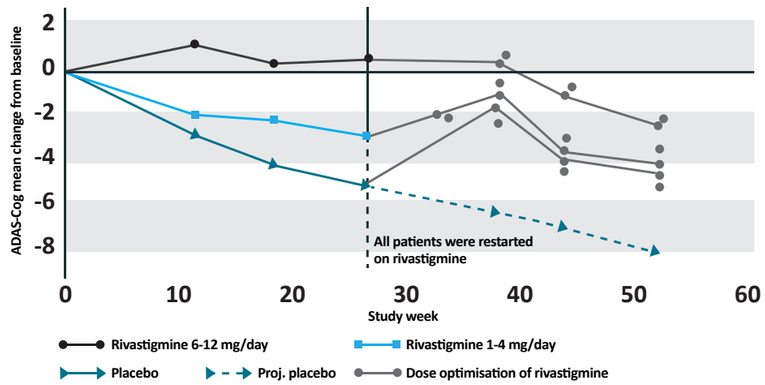
In secondary analysis, patients who were younger (<75 years) showed greater clinical benefit with rivastigmine treatment than those treated with donepezil according to ADCS-ADL and NPI.[16]

Notably, younger patients with two wild-type BuChE alleles showed a significantly greater response compared with donepezil, suggesting a differential effect of BuChE inhibition, in addition to AChE inhibition in these patients.[16]

ADCS-ADL: Alzheimer's Disease Cooperative Study-Activities of Daily Living; GDS: global deterioration Scale; ITT: intent to treat; LOCF: last observation carried forward; LS: Least squares; SE: standard error of the mean; NPI: Neuropsychiatric inventory.

Efficacy of rivastigmine (week 52 observed cases population) in patients with mild to moderately severe Alzheimer's disease

Efficacy of rivastigmine is maintained for at least one year of continuous treatment.



Graph adapted from Farlow M, et al. 2000.[17]

The delay in starting treatment, although it produces benefits, fails to match that of the group of patients treated with high doses from the beginning.

Delay in disease progression

Rivastigmine does not only offer **improvement in Alzheimer's symptoms*,** but may **also delay disease progression,** allowing patients to remain independent for longer.[5,6]

Rivastigmine **may be more beneficial in Alzheimer's patients with rapidly declining cognitive rates than those with slower decline.** These patients usually have a poor prognosis and higher mortality rates than patients experiencing slow progression.[6]

While the efficacy of donepezil is suggested to decrease with time due to its AChE upregulation, such reduction is not seen in rivastigmine efficacy.[8,18]

Zeyzelf® can offer cognitive benefits in your Alzheimer's patients, especially in those with rapid disease progression.[6]

*Cognitive function, memory, praxis and language deficiencies.
Based on the Alzheimer's Disease Assessment Scale - cognitive subscale.

Rivastigmine therapy in Alzheimer's dementia

Dual inhibition

Of the currently available cholinesterase inhibitors, **rivastigmine exhibits dual inhibitory activity** against both **acetylcholinesterase (AChE) and butylcholinesterase (BuChE).**[1]

Slowly reversible (pseudo-reversible) inhibition of AChE and BuChE by rivastigmine, targeting the G1 isoform of the AChE may lead to **greater, broader, and more sustained benefits** than rapidly reversible inhibition seen with donepezil.[19]

Persistent action and brain-region selectivity[18]

While the rapidly reversible medications like **donepezil, whose long-term use can lead to tolerance** due to their ability to upregulate AChE activity,[19] rivastigmine causes **persistent inhibition** of AChE and BuChE in **CSF as well as plasma**, as seen at 12 months of treatment in Alzheimer's patients (n=11).

Rivastigmine inhibition of both enzymes is greater in the CSF, than in the plasma. The percentage reductions in the CSF were highly correlated with those in the CSF at 3 and 12 months.

- AChE: **36%** reduction in the CSF and **27%** in the plasma
- BuChE: **45%** reduction in the CSF and **33%** in the plasma

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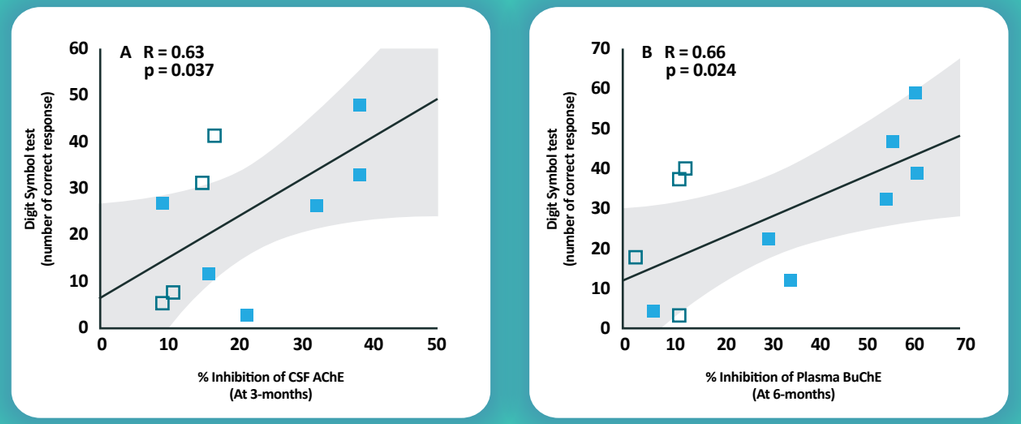
Inhibition of AChE and BuChE with rivastigmine is positively correlated with cognitive performance



Adapted from Darreh-Shori T, et al. 2002.[18]

Correlation between Attention Digital Symbol (Attention DS) test score and CSF AChE inhibition at 3 months (A) and correlation between test score and plasma BuChE inhibition at 6 months (B). Filled squares = oral rivastigmine higher dose group (10.5–12 mg/day; n=7); open squares = oral rivastigmine lower dose group (3–4.5 mg/day; n=4).

Preferential inhibition of the G1 isoform of AChE and also potentially BuChE may be responsible for the **brain-region selective targeted action of rivastigmine,** producing an effect in areas of the brain most impacted by AD.[8,19] On the other hand, **cholinesterase inhibitors that are not selective for particular isoforms may provide less targeted action.**[19]

AChE: acetylcholinesterase; BuChE: butylcholinesterase; CSF: cerebrospinal fluid.

Rivastigmine therapy in Alzheimer's dementia

Low potential for drug-drug interaction

Rivastigmine is metabolised to its metabolite NAP 226-90, which has minimal acetylcholinesterase inhibition and is excreted through the urine.[1,20]

Due to its **low accumulation potential and cytochrome P 450-independent metabolism,** rivastigmine has low potential for drug-drug interaction.

This lack of interaction has been confirmed with commonly prescribed medications in the elderly Alzheimer's patients including, anti-hypertensives, calcium-channel blockers, digoxin, diabetic drugs, nonsteroidal anti-inflammatory drugs, and oestrogens.[20]

Consider Zeyzelf® for your Alzheimer's patients for whom minimising interaction with other medications is a priority.[20]

Half-life

Rivastigmine is primarily metabolised by its target enzymes and the resulting inactive metabolite is renally excreted (low protein-binding).[1,8] While the mean apparent terminal elimination half-life ($t_{1/2}$) after the Zeyzelf® twice weekly patch removal is **8.06 h** for the 9.5 mg/24 h twice weekly patch,[1] donepezil remains **highly protein bound**, and has a **$t_{1/2}$ of ~70 hours**.[8]

Possibility of cessation of drug administration with Zeyzelf® by simply removing the patch.

Zeyzelf®

Switching patients to Zeyzelf® twice weekly transdermal patch

Patients can be simply switched to Zeyzelf® twice weekly from donepezil treatment

No washout period is required while switching your patients from donepezil to Zeyzelf® patches. **Immediate switch from donepezil to Zeyzelf® can be made** to avoid the potential washout-induced cognitive decline in patients.[8]

- **Switching** patients from donepezil to Zeyzelf® **without a wash-out period is well tolerated** and does not cause serious adverse events.[8]

Patients treated with rivastigmine capsules or oral solution can be switched to Zeyzelf® twice weekly as follows:[1]

- Patients on 3 mg/day or 6 mg/day oral dose, or those who did not tolerate 9 mg/day oral dose can be switched to the **initial dose of 4.6 mg/24 h** Zeyzelf® patch.
- **If the 4.6 mg/24 h patches are well tolerated for at least 4 weeks**, patients should be then switched to **9.5 mg/24 h, the recommended effective dose.***
- Patients on a stable and well tolerated oral dose of 9 mg/day or 12 mg/day can be switched to 9.5 mg/24 h Zeyzelf® patch.

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

*Patients with body weight < 50 kg and those with hepatic impairments may need careful dose titration and close monitoring for side effects.[1]

Application of Zeyzelf® patch and cover

Zeyzelf® transdermal patches should be applied twice weekly on fixed days (after four and three days, respectively)

You should change the patches on **two fixed days**	Monday and Friday OR Tuesday and Saturday OR Wednesday and Sunday OR Thursday and Monday OR Friday and Tuesday OR Saturday and Wednesday OR Sunday and Thursday

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of AD.[1]

Therapy should only be started if a caregiver is available to regularly administer and monitor the treatment.[1]

Recommended dosing:[1]

Initiation dose (for at least 4 weeks at the start of treatment): 4.6 mg/24 h

Maintenance dose: 9.5 mg/24 h

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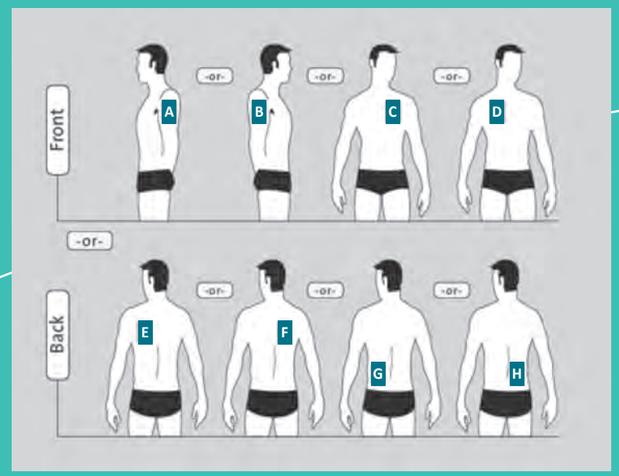
Patches should be applied to clean, dry, hairless, intact healthy skin on the upper or lower back, upper arm or chest, in a place which will not be rubbed by tight clothing[1]

It is not recommended to apply the transdermal patch to the thigh or abdomen due to its decreased bioavailability observed when applied to these areas of the body.[1]

Reapplication to the same area should be avoided for at least 2 weeks.[1]

Where to apply/application zones



The patches should be replaced at the same time of day. Before putting one new patch on, remove the previous patch and protective cover.

Replace the transdermal patches twice a week (on two fixed days); at the latest after 4 days and apply **one** new patch to **one** of the zones highlighted in the picture.

You can use the same zone (A or B or C or D or E or F or G or H), but do not use the same exact spot within the same zone. The breast should be avoided.

Patients and caregivers should be instructed on important administration instructions.[1] Please refer to the Summary of Product Characteristics or the Package leaflet: Information for the patient (Patient Information Leaflet) for further information on application of Zeyzelf® transdermal patches.

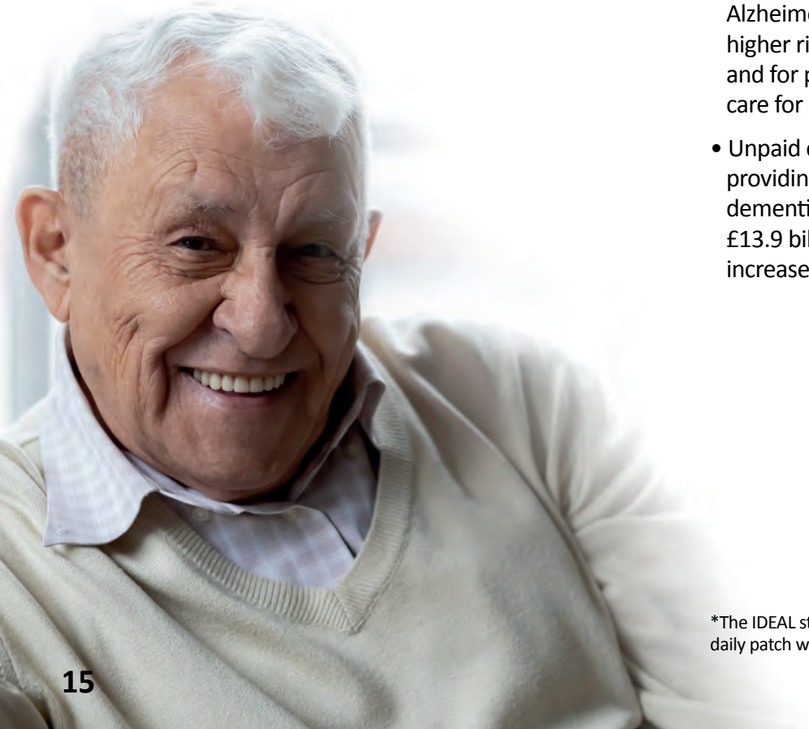
The cost of Alzheimer's dementia

Cost and disease burden of dementia

The total cost of dementia to the UK is currently £34.7 billion a year and is made up of healthcare costs (costs to the NHS), social care costs (costs of homecare and residential care), and costs of unpaid care (provided by family members).[29] With the average annual cost of £32,250 per person with dementia, the cost of the drug prescription represents a very small proportion. Reducing carer burden and time is essential.[21]

In the UK, there is a considerable economic cost associated with dementia estimated at £23 billion a year, which is projected to reach around £70 billion by 2029.[22, 23]

- **1 in 14** people over 65 have dementia in the UK.[24]
- **1/4** of hospital beds are occupied by people living with dementia who are over 65.[25]



Cost to carers

Patient and caregiver satisfaction are essential for good adherence to treatment.[26]

> 70% of 1,059 caregivers preferred transdermal patches to capsules overall*. Carers preferred the patch over capsules for:[26]

- the ease of use (p<0.0001) and
- the ease of following the schedule (p<0.0001)

Carers also reported greater satisfaction (p<0.0001) and less interference with daily life (p<0.01) with patches compared with the capsules.[26]

Alzheimer's dementia, like other dementias, generates a significant burden on family members and/or caregivers.[27]

- 1 in 3 people will care for someone with dementia in their lifetime.[22]
- Family and caregivers of people with Alzheimer's and related dementias have a higher risk for developing anxiety, depression, and for poorer quality of life than those who care for people with other conditions.[27]
- Unpaid carers, or families and friends providing care to their loved ones with dementia, are providing care valued at £13.9 billion a year. This is expected to increase to £35.7 billion by 2040.[21]

*The IDEAL study compared rivastigmine once daily patch with the capsule.[26]

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Cost of Zeyzelf®

Zeyzelf® is less costly compared to the original transdermal patch, Exelon®, with over 50% cost savings[28]

	NHS List Price for 28 days treatment (£)		NHS Saving
Product	Zeyzelf® twice weekly transdermal patch 8 patches	Exelon® daily transdermal patch 28 patches	
4.6 mg/24 hr	35.09	72.77	52%
9.5 mg/24 hr	35.09	72.77	52%

* A pack of Exelon® transdermal patches contains 30 patches and costs £77.97[28]

Zeyzelf® tolerability profile

Zeyzelf® twice weekly transdermal patches are generally well tolerated[1,3]

Application site reactions (usually mild to moderate erythema) and gastrointestinal disorders are the most frequent AEs observed with the use of Zeyzelf® transdermal patches[1]

Common adverse reactions reported in 1,670 patients with Alzheimer's dementia treated in randomised, double-blind, placebo and active-controlled clinical studies with rivastigmine transdermal patches for a duration of 24-48 weeks and from post-marketing data.[1]

Common (in 1–10% patients) adverse events (AEs) associated with Zeyzelf® patches:[1]

General disorders and administration site conditions	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, and weight decreased
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, dyspepsia, and abdominal pain
Infection and infestations	UTI
Metabolism and nutrition disorders	Anorexia and reduced appetite
Psychiatric disorders	Anxiety, depression, delirium, and agitation
Nervous system disorders	Headache, syncope, and dizziness
Skin and subcutaneous tissue disorders	Rash
Renal and urinary disorders	Urinary incontinence

The following Adverse Reactions have only been observed with oral rivastigmine and not with the twice weekly patches:[1]

Common	Confusion, malaise, increased sweating
Rare	Duodenal ulcers and angina pectoris
Very rare	Gastrointestinal haemorrhage
Not known	Some cases of severe vomiting associated with oesophageal rupture

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Summary

Benefits of Zeyzelf® twice weekly transdermal patches:

Efficacy/Mode of Action

- Achieving high-dose efficacy without compromising safety[2–4]
- Delay in disease progression[5]
- Sustained, brain region-specific efficacy[18,19]
- Dual inhibition of AChE and BuChE[18]
- Long-term use does not lead to tolerance[18]

Practical benefits for patients

- Improved compliance vs oral medications[10,11]
- Reduces pill burden in patients on polypharmacy
- An alternative treatment option for patients who may not be tolerating, or are averse to, or have trouble swallowing their current orally delivered AChE inhibitor[4]
- Better adhesion than single day patch*[3]

Tolerability

- Skin irritability comparable to other rivastigmine transdermal patches [1,30,31]
- Low potential for drug-drug interaction with commonly prescribed medications for comorbidities[1,20]
- Lower risk of side effects like vomiting and nausea due to avoidance of the gastrointestinal route and reduced fluctuations of plasma drug levels vs the oral formulation[2]
- Lower risk of toxicity and dose dumping vs the oral route of administration[10,11]

*Compared with Exelon® in a randomised clinical trial.[3]

Local resources

Here's a list of some useful resources that may be helpful for your patients and their caregivers in understanding Alzheimer's dementia, its treatment and management:

ALZHEIMER'S SOCIETY:
www.alzheimers.org.uk

ALZHEIMER'S RESEARCH UK:
www.alzheimersresearchuk.org

DEMENTIA UK:
www.dementiauk.org/information-and-support/types-of-dementia/alzheimers-disease/

THE SCOTTISH DEMENTIA WORKING GROUP (SDWG):
www.alzscot.org

THE ALZHEIMER'S SOCIETY (INCLUDING DEMENTIA FRIENDS):
www.dementiafriends.org.uk

CARERS UK (TO CONNECT WITH OTHER CARERS):
www.carersuk.org

Zeyzelf®

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Zeyzelf (rivastigmine) Twice Weekly Transdermal Patches Prescribing Information.
Please refer to the Zeyzelf Summary of Product Characteristics (SmPC) for full details.

Presentations: Transdermal patches each releasing either 4.6 mg or 9.5mg of rivastigmine per 24 hours. **Indication:** Symptomatic treatment of mild to moderately severe Alzheimer's dementia. **Dosage and administration:** Zeyzelf twice weekly transdermal patches should be applied twice weekly on fixed days (after four and three days, respectively). Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's dementia. Similar to any treatment initiated in patients with dementia, therapy with rivastigmine should only be started if a caregiver is available to regularly administer and monitor the treatment. Dosage: *Initial dose:* Treatment is started with 4.6 mg/24 h. *Maintenance dose:* After a minimum of four weeks of treatment and if well tolerated according to the treating physician, the dose of 4.6 mg/24 h should be increased to 9.5 mg/24 h, the daily recommended effective dose, which should be continued for as long as the patient continues to demonstrate therapeutic benefit. *Dose escalation:* 9.5 mg/24 h is the recommended daily effective dose which should be continued for as long as the patient continues to demonstrate therapeutic benefit. If well tolerated and only after a minimum of six months of treatment at 9.5 mg/24 h, the treating physician may consider increasing the dose to 13.3 mg/24 h in patients who have demonstrated a meaningful cognitive deterioration while on the recommended daily effective dose of 9.5 mg/24 h. The 13.3 mg/24 h dose strength cannot be achieved with Zeyzelf twice weekly. Treatment should be temporarily interrupted if gastrointestinal adverse reactions are observed until these adverse reactions resolve. Transdermal patch treatment can be resumed at the same dose if treatment is not interrupted for more than three days. Otherwise treatment should be re-initiated with 4.6 mg/24 h. *Switching from capsules or oral solution to transdermal patches:* Refer to SmPC. **Special populations:** Patients with body weight below 50 kg: Particular caution should be exercised in titrating patients with body weight below 50 kg above the recommended effective dose of 9.5mg/24 h. Hepatic impairment: In mild to moderate hepatic impairment 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. have not been studied. Particular caution should be exercised in titrating patients with severe hepatic impairment. Renal impairment: No dose adjustment is necessary for patients with renal impairment. **Method of administration:** Zeyzelf twice weekly is for transdermal use. Transdermal patches should be applied twice weekly on fixed days (after four and three days, respectively) to clean, dry, hairless, intact healthy skin on the upper or lower back, upper arm or chest, in a place which will not be rubbed by tight clothing. It is not recommended to apply the transdermal patch to the thigh or to the abdomen due to decreased bioavailability of rivastigmine observed when the transdermal patch is applied to these areas of the body. The transdermal patch should not be applied to skin that is red, irritated or cut. Reapplication to the exact same skin location within 14 days should be avoided to minimise the potential risk of skin irritation. To prevent interference with the adhesive properties of the transdermal patch, no cream, lotion or powder should be applied to the skin area where the medicinal product is to be applied. **Patients and caregivers should be instructed on important administration instructions:** Refer to SmPC. **Common Adverse Reactions:** 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. List of common adverse reactions reported in 1,670 patients with Alzheimer's dementia treated in randomised, double-blind, placebo and active-controlled clinical studies with rivastigmine transdermal patches for a duration of 24-48 weeks and from post-marketing data: Urinary tract infection. Anorexia, decreased appetite Anxiety, depression, delirium, agitation. Headache, syncope, dizziness. Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain. Rash. Urinary incontinence. Application site skin reactions (application site erythema, pruritus, oedema, dermatitis, irritation), asthenic conditions (e.g. fatigue, asthenia), pyrexia, weight decreased. **Please consult the full SmPC for other adverse reactions. Contraindications:** Hypersensitivity to the active substance rivastigmine, to other carbamate derivatives or to any other excipients. Previous history of application site reactions suggestive of allergic contact dermatitis with rivastigmine patch. **Warnings and Precautions:** Zeyzelf twice weekly transdermal patches are multiday patches. Care should be exercised and application of more than one patch at the same time should be avoided. The incidence and severity of adverse reactions generally increase with increasing doses, particularly at dose changes. If treatment is interrupted for more than three days, it should be re-initiated with 4.6 mg/24 h. *Misuse of the medicinal product and dosing errors resulting in overdose:* Misuse of the medicinal product and dosing errors with rivastigmine transdermal patch have resulted in serious adverse reactions; some cases have required hospitalisation, and rarely led to death. Patients and their caregivers must be instructed on important administration instructions for rivastigmine transdermal patch. *Gastrointestinal disorders:* Gastrointestinal disorders such as nausea, vomiting and diarrhoea are dose related, and may occur when initiating treatment and/or increasing the dose. These adverse reactions occur more commonly in women. *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. *Bradycardia:* Rivastigmine may cause bradycardia which constitutes a risk factor in the occurrence of torsade de pointes, predominantly in patients with risk factors. *Care must be taken when prescribing Zeyzelf twice weekly transdermal patches to patients* with sick sinus syndrome or conduction defects (sino-atrial block, atrio-ventricular block); patients with active gastric or duodenal ulcers or patients predisposed to these conditions because rivastigmine may cause increased gastric secretions; patients predisposed to urinary obstruction and seizures because cholinomimetics may induce or exacerbate these diseases; 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. In these cases, treatment should be discontinued. 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 Zeyzelf twice weekly 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. **Interactions: Refer to the SmPC for full details.** Rivastigmine may exaggerate the effects of succinylcholine-type muscle relaxants during anaesthesia. Caution is recommended when selecting anaesthetic agents. Possible dose adjustments or temporarily stopping treatment can be considered if needed. Rivastigmine should not be given concomitantly with other cholinomimetic substances. Rivastigmine might interfere with the activity of anticholinergic medicinal products (e.g. oxybutynin, tolterodine). Caution should be exercised when rivastigmine is combined with beta-blockers and other bradycardia medicinal products (e.g.class III antiarrhythmic medicinal products, calcium channel antagonists, digitalis glycoside, pilocarpin). The combination of rivastigmine with torsades de pointes-inducing medicinal products should be observed with caution and clinical monitoring (ECG) may also be required. **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.

Marketing Authorisation Number and Basic NHS Price:
Zeyzelf twice weekly 4.6 mg/24 h transdermal patch PLGB 50827/0023 (8 patches: £35.09);

Zeyzelf twice weekly 9.5 mg/24 h transdermal patch PLGB 50827/0024 (8 patches: £35.09).

Marketing Authorisation Holder: Luye Pharma Ltd. 40 Occam Road, Guildford, GU2 7YG, United Kingdom.
Legal Category: POM.
Further information: Luye Pharma Ltd., 40 Occam Road, Guildford, GU2 7YG. info@luyepharma.co.uk
Date of preparation: February 2024.
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Adverse events should be reported.
Reporting forms and information can be found at: https://yellowcard.mhra.gov.uk/
Adverse events should also be reported to Luye Pharma Ltd at safety@luyepharma.co.uk

For further information please visit:
www.luye.co.uk

Luye Pharma Ltd
Surrey Technology Centre
Guildford
Surrey GU2 7YG

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