New Zealand Data Sheet

1 RIVASTIGMINE PATCH BNM

RIVASTIGMINE PATCH BNM 5 (4.6 mg/24 h) and
RIVASTIGMINE PATCH BNM 10 (9.5 mg/24 h) transdermal patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

RIVASTIGMINE PATCH BNM 5: Each transdermal patch of 4.6 cm^2 contains 6.9 mg of rivastigmine, releasing 4.6 mg of rivastigmine per 24 hours.

RIVASTIGMINE PATCH BNM 10: Each transdermal patch of 9.2 cm^2 contains 13.8 mg of rivastigmine, releasing 9.5 mg of rivastigmine per 24 hours.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Transdermal patch

Each transdermal patch is a thin, matrix-type transdermal patch of a circular shape. The outside of the backing layer is tan coloured.

RIVASTIGMINE PATCH BNM 5**:** Each patch is printed in orange with "RIV-TDS 4.6 mg/24 h".

RIVASTIGMINE PATCH BNM 10: Each patch is printed in orange with "RIV-TDS 9.5 mg/24 h".

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of patients with mild to moderately severe dementia of the Alzheimer's type (also termed probable Alzheimer's disease or Alzheimer's disease)

4.2 Dose and method of administration

Dose

Initial dose and dose titration to the effective dose:

Treatment is started with Rivastigmine Patch BNM 5 once a day.

After a minimum of four weeks of treatment and if well tolerated, this dose should be increased to Rivastigmine Patch BNM 10, which is the recommended effective dose to be continued for as long as a therapeutic benefit for the patient exists.

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 Rivastigmine Patch BNM 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:

Patients treated with rivastigmine capsules may be switched to Rivastigmine Patch BNM as follows:

- A patient who is on a dose of < 6 mg per day oral rivastigmine can be switched to Rivastigmine Patch BNM 5.
- A patient who is on a dose of 6 to 12 mg per day oral rivastigmine may be directly switched to Rivastigmine Patch BNM 10.

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

Method of administration

Rivastigmine Patch BNM 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 with 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 (see Section 4.4 Special warnings and precautions for use and Section 4.9 Overdose).

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 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, on 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. Patients and caregivers should be instructed accordingly.

Immediately after removing the patch, patients or caregivers must wash their hands with soap and water. In case of contact with eyes or if the eyes become red after handling the patch, patients or caregivers must rinse the area immediately with plenty of water, and seek medical advice if symptoms do not resolve.

Special population

Patients with body weight below 50 kg

Caution should be exercised in titrating these patients as they may experience more adverse reactions and may be more likely to discontinue due to adverse events. Particular caution should be exercised in titrating and monitoring these patients for adverse reactions (e.g. excessive nausea or vomiting) and consider reducing the dose if such adverse reactions develop (see Section 4.4 Special warnings and precautions for use).

Paediatric patients

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

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 might experience more adverse events. Particular caution should be exercised in titrating these patients above the recommended maintenance dose of Rivastigmine Patch BNM 10 (see Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties).

Renal impairment

No dose adjustment is necessary for patients with renal impairment (see Section 5.2 Pharmacokinetic properties).

4.3 Contraindications

The use of Rivastigmine Patch BNM is contraindicated in patients with:

- Known hypersensitivity to rivastigmine, other carbamate derivatives or other ingredients of the formulation (see Section 6.1 List of excipients).
- Previous history of application site reactions suggestive of allergic contact dermatitis with rivastigmine transdermal patch (see Section 4.4 Special warnings and precautions for use – Application site reactions and skin reactions).

4.4 Special warnings and precautions for use

Medication misuse and dosing errors resulting in overdose

Medication misuse and dosing errors with rivastigmine patches have resulted in serious adverse reactions; some cases have required hospitalisation, and rarely led to death (see Section 4.9 Overdose). The majority of medication misuse and dosing errors have involved not removing the old patch when putting on a new one and the use of multiple patches at one time. Patients and their caregivers must be instructed on important administration instructions for Rivastigmine Patch BNM (see Section 4.2 Dose and method of administration).

Gastrointestinal disorders

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 Rivastigmine Patch BNM 5.

Gastrointestinal disorders such as nausea, vomiting and diarrhoea may occur when initiating treatment and/or increasing the dose. They may respond to a dose reduction. In other cases, use of Rivastigmine Patch BNM 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 4.8 Undesirable effects).

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 Patch BNM.

Other adverse reactions from increased cholinergic activity

As with other cholinergic substances care must be taken when prescribing Rivastigmine Patch BNM to patients:

- with sick sinus syndrome or conduction defects (sino-atrial block, atrio-ventricular block) (see Section 4.8 Undesirable effects).
- with active gastric or duodenal ulcers or patients predisposed to these conditions because gastric acid secretions may be increased.
- predisposed to urinary obstruction and seizures because cholinomimetics may induce or exacerbate these diseases.
- with a history of asthma or obstructive pulmonary disease.

Like other cholinomimetics, rivastigmine may induce or exacerbate extrapyramidal symptoms.

Application site reactions and skin reactions

Skin application site reactions may occur with Rivastigmine Patch BNM and are usually mild or moderate in intensity (see Section 4.8 Undesirable effects – Application site reactions). 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, 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 4.3 Contraindications).

In patients who develop application site reactions suggestive of allergic contact dermatitis to Rivastigmine Patch BNM 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 sensitised to rivastigmine by exposure to rivastigmine patch may not be able to take rivastigmine in any form.

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 4.3 Contraindications). Patients and caregivers should be instructed accordingly.

Special populations

Patients with body weight below 50 kg

Patients with body mass below 50 kg may experience more adverse reactions and may be more likely to discontinue due to adverse events. Carefully titrate and monitor these patients for adverse reactions (e.g. excessive nausea or vomiting) and consider reducing the dose if such adverse reactions develop (see Section 4.2 Dose and method of administration).

Paediatric patients

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

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. Particular caution should be exercised in titrating these patients (see Section 4.2 Dose and method of administration and Section 5.2 Pharmacokinetic properties).

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been conducted with Rivastigmine Patch BNM.

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, 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.

4.6 Fertility, pregnancy and lactation

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 Rivastigmine Patch BNM 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.

Breastfeeding

In animals, rivastigmine and/or metabolites were excreted in breast milk. It is not known if Rivastigmine Patch BNM is excreted into human milk, and patients on Rivastigmine Patch BNM 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. There is no information available on the effects of rivastigmine on human fertility.

4.7 Effects on ability to drive and use machines

Alzheimer'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.

4.8 Undesirable effects

The overall incidence of adverse events in patients treated with rivastigmine patch 9.5 mg/24 hours was lower than the rate in patients who received rivastigmine capsule treatment. Nausea and vomiting were the most common adverse events in patients who received active treatment, and occurred at similar rates in both rivastigmine patch 17.4 mg/24 hours and capsule groups. However, the rates of both of these events were substantially lower with rivastigmine patch 9.5 mg/24 hours group. The most commonly reported adverse drug reactions are gastrointestinal including nausea and vomiting, especially during titration.

Adverse reactions 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.

Adverse drug reactions reported in 2687 patients with Alzheimer's dementia treated for 24 weeks to 48 weeks in randomised controlled clinical studies with rivastigmine patches at all doses.

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

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. haemorrhagic duodenitis)

Renal and urinary disorders
Common: Urinary incontinence

Skin and subcutaneous tissue disorders
Uncommon: Hyperhidrosis

General disorders and administration site conditions
Common: Application site reactions, application site erythema**, application site pruritus, application site oedema**, fatigue, asthenia
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".*

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, seizure. Worsening of Parkinson's disease has been observed in patients with Parkinson's disease who were treated with rivastigmine patches**.**

Frequency not known: Hepatitis, restlessness, sick sinus syndrome, allergic dermatitis (disseminated), extrapyramidal symptoms in patients with Alzheimer's dementia, tremor, nightmares.

Information from clinical trials in patients with Alzheimer's dementia treated with rivastigmine patches

The adverse drug reactions in Table 1 were reported in patients with mild to moderate Alzheimer's dementia treated with rivastigmine patches.

Table 1:
Adverse drug reactions (≥ 2% in all rivastigmine patch groups) from the 24-week double-blind placebo controlled clinical trial conducted with rivastigmine patches in patients with mild to moderate Alzheimer's dementia

	Rivastigmine patch 9.5 mg/24 hours group n (%)	Rivastigmine patch 17.4 mg/24 hours group n (%)	Rivastigmine capsules 12 mg/day n (%)	Placebo n (%)	All Rivastigmine 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)

Application site reactions (skin irritation)
In double-blind controlled clinical trials, application site reactions were mostly mild to moderate in severity. The incidence of application site skin reactions leading to discontinuation was observed in ≤ 2.3% of rivastigmine patch patients. This number was 4.9% and 8.4% in the Chinese population and Japanese population, respectively.

Cases of skin irritation were captured separately on an investigator-rated skin irritation scale. Skin irritation, when observed, was mostly slight or mild in severity and was rated as severe in ≤ 2.2 % of rivastigmine patch patients in a double-blind controlled study and in ≤ 3.7 % of rivastigmine patch patients in a double-blind controlled study in Japanese patients. See Section 4.4 Special warnings and precautions for use – Application site reactions and skin reactions.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 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.

Overdose with rivastigmine 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 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 Patch BNM 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 iv atropine sulphate is recommended, with subsequent doses based on clinical response. Use of scopolamine as an antidote is not recommended.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Brain-selective cholinesterase inhibitor
ATC code: N06DA03

Mechanism of action

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 Patch BNM 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.

5.2 Pharmacokinetic properties

Absorption

Absorption of rivastigmine from rivastigmine 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 of rivastigmine patch 4.6 mg/24 hours to rivastigmine patch 17.4 mg/24 hours. Although less pronounced than with the oral formulation, exposure to rivastigmine (C_{max} and AUC) increased over-proportionally with rising patch doses. Escalating from rivastigmine patch 4.6 mg/24 hours to rivastigmine patch 17.4 mg/24 hours, the increase in rivastigmine AUC relative to the lowest dose of rivastigmine patch 4.6 mg/24 hours was 2.6, 4.9 and 7.8-fold for rivastigmine patch 9.5 mg/24 hours, rivastigmine patch 13.3 mg/24 hours and rivastigmine patch 17.4 mg/24 hours, respectively. 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 modelling the rivastigmine patch 17.4 mg/24 hours exhibited exposure (AUC_{24h}) in a typical patient equivalent to that which would be provided by an oral dose of about 9 to 10 mg twice daily (i.e. 18 to 20 mg/day), while rivastigmine patch 9.5 mg/24 hours 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**

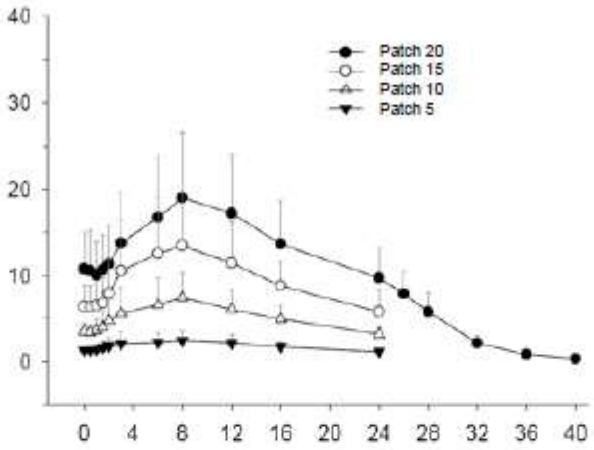
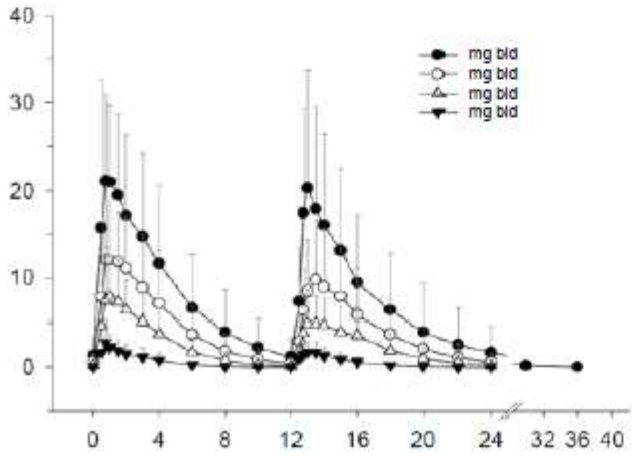


Figure 2 **Rivastigmine plasma concentrations following oral (twice daily) capsule**



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 4.2 Dose and method of administration).

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.

Biotransformation

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 t½ 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 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 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.

Special populations

Elderly subjects

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

Subjects with hepatic impairment

No study was conducted with the rivastigmine 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 4.2 Dose and method of administration and Section 4.4 Special warnings and precautions for use).

Subjects with renal impairment

No study was conducted with the rivastigmine 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 4.2 Dose and method of administration).

Clinical studies

Alzheimer's dementia

The efficacy of rivastigmine patches (9.5 mg/24 hours, 13.3 mg/24 hours and 17.4 mg/24 hours) in patients with mild to moderately severe dementia of the Alzheimer's type 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.

Mild to Moderate Alzheimer's dementia

24-week placebo-controlled study

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), 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 2.

The results for clinically relevant responders from the 24-week study are provided in Table 3. Clinically relevant improvement was defined a priori as at least 4-point improvement on the ADAS-cog, no worsening on the ADCS-CGIC, and no worsening on the ADCS-ADL.

Table 2:
24-week results for the three assessment tools in patients with mild to moderate Alzheimer's dementia

ITT-LOCF population	**Rivastigmine patch 9.5 mg/24 hours N = 251**	**Rivastigmine patch 17.4 mg/24 hours N = 264**	**Rivastigmine capsule 12 mg/day N = 256**	**Placebo N = 282**
ADAS-Cog				
	(n=248)	(n=262)	(n=253)	(n=281)
Mean baseline ± SD	27.0 ± 10.3	27.4 ± 9.7	27.9 ± 9.4	28.6 ± 9.9
Mean change at week 24 ± SD	-0.6 ± 6.4	-1.6 ± 6.5	-0.6 ± 6.2	1.0 ± 6.8
p-value versus placebo	0.005[*1]	<0.001[*1]	<0.003[*1]	
ADCS-CGIC				
	(n=248)	(n=260)	(n=253)	(n=278)
Mean score ± SD	39.0 ± 1.20	4.0 ± 1.27	3.9 ± 1.25	4.2 ± 1.26
p-value versus placebo	0.010[*2]	0.054[2]	0.009[*2]	
ADCS-ADL				
	(n=247)	(n=263)	(n=254)	(n=281)
Mean baseline ± SD	50.1 ± 16.3	47.6 ± 15.7	49.3 ± 15.8	49.2 ± 16.0
Mean change at week 24 ± SD	-0.1 ± 9.1	0.0 ± 11.6	-0.5 ± 9.5	-2.3 ± 9.4
p-value versus placebo	0.013[*1]	0.017[*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.

Table 3:
Results for clinically relevant responders form the 24-week placebo-controlled study in patients with mild to moderate Alzheimer's dementia

	Patients with clinically significant response (%)			
	Rivastigmine patch 9.5mg/24 hours	Rivastigmine patch 17.4 mg/24 hours	Rivastigmine capsule 12 mg/day	Placebo
At least 4 points improvement on ADAS-Cog with no worsening on ADCS-CGIC and ADCS-ADL	17.4*	20.2**	19.0**	10.5

$^{*}p<0.05$, $^{**}p<0.01$ versus placebo

Similar results were observed with rivastigmine patch 9.5 mg/24 hours in separately conducted controlled studies in Chinese and Japanese patients with mild to moderately severe Alzheimer's dementia.

48-week active comparator controlled study

Patients involved in the active comparator controlled study had an initial baseline MMSE (Mini-Mental State Examination) score of 10–24. The study was designed to compare the efficacy of the rivastigmine patch 13.3 mg/24 hours versus the rivastigmine patch 9.5 mg/24 hours during a 48-week double blind treatment phase in Alzheimer's disease patients who demonstrated functional and cognitive decline after an initial 24-48 week open-label treatment phase while on a maintenance dose of rivastigmine patch 9.5 mg/24 hours. Functional decline was assessed by the investigator and cognitive decline was defined as a decrease in the MMSE score of $\geq$2 points from the previous visit or a decrease of $\geq$3 points from baseline. Efficacy was established by the use of independent, domain-specific assessment tools which were applied at regular intervals during the 48-week treatment period. These include the ADAS-Cog (a performance-based measure of cognition) and the ADCS-instrumental ADL (a subscale from the ADCS-ADL activities of daily living scale assessing instrumental activities which are thought to involve more complex cognitive activities and represent clinically meaningful functional activities of daily living, which include maintaining finances, meal preparation, shopping, ability to orient oneself to surroundings, able to be left unattended, etc.). The 48-week results for the two assessment tools are summarized in Table 4.

Table 4:
Mean change from double blind baseline in ADAS-Cog and ADCS-IADL scores over time in patients with mild to moderate Alzheimer's dementia

Population visit		Rivastigmine patch 13.3 mg/24 hours N = 265	Rivastigmine patch 9.5 mg/24 hours N = 271	Rivastigmine patch 13.3 mg/24 hours – 9.5 mg/24 hours		
		Mean	Mean	DLSM	95% CI	p-value
ADAS-Cog LOCF	Baseline	(n=264) 34.4	(n=268) 34.9			
DB-week 12	Value	34.2	35.5			
	Change	-0.2	0.6	-0.9	(-2.0, 0.1)	0.091
DB-week 24	Value	35.4	37.1			
	Change	1.0	2.2	-1.3	(-2.5, -0.2)	0.027*
DB-week 48	Value	38.5	39.7			
	Change	4.1	4.9	-0.8	(-2.1, -0.5)	0.227
ADCS-IADL LOCF	Baseline	(n=265) 27.5	(n=271) 25.8			
Week 8	Value	27.3	25.0			
	Change	-0.2	-0.8	0.8	(-0.2, 1.9)	0.114
Week 12	Value	27.5	25.4			
	Change	0.1	-0.4	0.7	(-0.5, 1.8)	0.252
Week 16	Value	26.7	24.0			
	Change	-0.7	-1.8	1.3	(0.2, 2.5)	0.025*
Week 24	Value	26.0	22.9			
	Change	-1.5	-2.8	1.7	(0.5, 2.9)	0.005*
Week 32	Value	25.2	21.7			
	Change	-2.2	-4.0	2.1	(0.9, 3.4)	<0.001*
Week 48	Value	23.1	19.6			
	Change	-4.4	-6.2	2.2	(0.8, 3.6)	0.002*

ANCOVA – analysis of covariance, CI – confidence interval, DB – double blind
DLSM – difference in least square means, LOCF – Last Observation Carried Forward
ADAS-cog scores: A negative difference in DLSM indicates greater improvement in rivastigmine patch 13.3 mg/24 hours as compared to rivastigmine patch 9.5 mg/24 hours
ADCS-IADL scores: A positive difference in DLSM indicates greater improvement in rivastigmine patch 13.3 mg/24 hours as compared to rivastigmine patch 9.5 mg/24 hours
n = number of patients with an assessment at baseline and the corresponding visit.
The DLSM, 95% CI, and p-value are based on an ANCOVA model adjusted for country and baseline
**p < 0.05*

5.3 Preclinical safety data

Acute toxicity
The estimated oral LD50 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 and chromosomal damage *in vivo*. 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 4.6 Fertility, pregnancy and lactation). Specific dermal studies in pregnant animals have not been conducted.

Local tolerance
Rivastigmine patches were not phototoxic and are 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 Rivastigmine Patch BNM to induce mild erythema in patients. A mild eye/mucosal irritation potential of rivastigmine was identified in a rabbit study (see Section 4.2 Dose and method of administration - Important administration instructions).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

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

Release liner:
- polyester film, fluoropolymer-coated

Orange printing ink

6.2 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 Rivastigmine Patch BNM is to be applied.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C.

Keep the patch in the sachet until use.

6.5 Nature and contents of container

Each child-resistant sachet is made of a paper / polyethylene terephthalate / aluminium / polyacrylnitrile multilaminated material or paper / polyethylene terephthalate / polyethylene / aluminium / LasPolD. One sachet contains one transdermal patch. Each transdermal patch is protected by a cover sheet made of siliconised polyethylene terephthalate film.

Available in packs containing 30 sachets.

6.6 Special precautions for disposal

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

Any used or unused transdermal patches should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

BNM Group
39 Anzac Road
Browns Bay
Auckland 0753

Phone 0800 565 633

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 06 June 2019

10 DATE OF REVISION OF TEXT

25 February 2021

Summary table of changes

Section changed	Summary of new information
4.5	Addition of new packaging material