Rivastigmine Transdermal System (Exelon® Patch—Novartis)
AHFS 12:04, Parasympathomimetic (Cholinergic) Agents

Table of Contents

Executive Summary 2

Introduction 3
Table 1. Outcome Measures of Standard Tests Used in Evaluating AD Patients 3

Pharmacology 4

Pharmacokinetics 4
Table 2. Pharmacokinetic Comparison of Transdermal and Oral Rivastigmine 5
Special Populations 5

Clinical Efficacy 5
Table 3. Clinical Trials of Rivastigmine Transdermal System vs. Rivastigmine Oral in Alzheimer Disease Patients 7

Adverse Drug Reactions 8
Table 4. Discontinuation Rates as Presented in Product Labeling 8
Table 5. Patients (%) with Adverse Drug Reactions with a Frequency ≥ 2% and at a Rate Exceeding Placebo 8

Drug Interactions 8

Dosage and Administration 9
Monitoring 9

Critical Issues 9

Summary 10

References 10

Document Information 12

Appendix: Grades of Scientific Evidence 12

Rivastigmine Transdermal System (Exelon® Patch—Novartis)
AHFS 12:04, Parasympathomimetic (Cholinergic) Agents

Executive Summary

Introduction: Rivastigmine transdermal system is labeled for treatment of mild to moderate dementia of Alzheimer disease (AD) and Parkinson disease (PD). Rivastigmine has been available orally since 2000. Rivastigmine transdermal and oral are the only medications labeled for dementia of PD. Rivastigmine treats symptoms and does not prevent progression of disease.

Pharmacology / Pharmacokinetics: Rivastigmine is a reversible cholinesterase inhibitor which acts centrally to enhance cholinergic function by increasing acetylcholine levels. Rivastigmine has a ten-fold greater affinity for brain acetylcholinesterase than for peripheral forms of the enzyme. However, as AD progresses and fewer cholinergic neurons remain, the beneficial effects of rivastigmine may diminish. Extent of absorption is site-specific. Steady-state plasma concentration is related to body weight. Rivastigmine transdermal facilitates steadier delivery of rivastigmine compared to oral. Plasma elimination half-life is approximately 3 hours following patch removal.

Clinical Efficacy: A single phase III controlled-trial compared rivastigmine transdermal system to the oral rivastigmine formulation and to placebo in patients with AD. The 9.5 mg/24 hr patch was significantly better than placebo on the ADAS-Cog ($p=0.005$) and ADCS-CGIC ($p=0.01$) evaluations. The overall clinical effectiveness of rivastigmine transdermal in dementia of AD, as with other members of its class, is modest. The percent of patients in each group who achieved a clinically meaningful decrease of at least 4 units from baseline on the ADAS-Cog were 27.4% for the 9.5 mg/24 hours patch, 28.5% for the 6 mg twice-daily capsule, and 19.9% for placebo ($p < 0.05$ all groups vs. placebo). Rivastigmine transdermal demonstrated non-inferiority to rivastigmine oral. Transdermal rivastigmine is labeled for dementia of PD based on bioequivalence with the oral formulation.

Adverse Drug Reactions / Drug Interactions: Common adverse drug reactions reported in the single controlled clinical trial include nausea, vomiting, and diarrhea. Nausea and vomiting were cited as the adverse effects most commonly leading to discontinuation of treatment. Inducers or inhibitors of CYP450 metabolism are not expected to affect the metabolism of rivastigmine. Concomitant use of rivastigmine with other cholinesterase inhibitors, cholinomimetic medications, or neuromuscular blocking agents is not recommended.

Dosage and Administration: Initiate rivastigmine transdermal system with the 4.6 mg/24 hour patch applied once daily. After four weeks the dose may be titrated upward to the recommended effective dose of 9.5 mg/24 hours if the initial dose is well tolerated. Do not exceed 9.5 mg/24 hours. Administer and titrate dose cautiously in patients weighing less than 50 kg. No dosage adjustments are necessary for age, or for hepatic or renal impairment. Titrate dose according to individual tolerability.

Summary: Rivastigmine transdermal offers a once daily therapeutic alternative to oral cholinesterase inhibitors in the treatment of dementia of AD and of PD. This dosage form may most benefit patients with dysphagia or caregivers who prefer this method of administration.

Rivastigmine Transdermal System (Exelon® Patch—Novartis)
AHFS 12:04, Parasympathomimetic (Cholinergic) Agents

Introduction

Rivastigmine transdermal system is labeled for the treatment of mild to moderate dementia of Alzheimer disease (AD) and mild to moderate dementia of Parkinson disease (PD).[1] Rivastigmine belongs to the class of drugs known as cholinesterase inhibitors and has been available in an oral formulation since 2000.[1] Rivastigmine transdermal system is the first skin patch approved for use in the treatment of AD. Rivastigmine transdermal and oral are the only medications labeled for treatment of Parkinson's-associated dementia.[2] Rivastigmine does not prevent disease progression, but treats the symptoms of the disease.[1, 3]

This review presents efficacy and safety data for rivastigmine transdermal system. Comparative data for the oral formulation of rivastigmine is presented as well. There are no studies available comparing rivastigmine transdermal systems with oral cholinesterase inhibitors other than rivastigmine oral.

Table 1 summarizes common outcome measures used in clinical studies and general practice. These outcome measures are used to assess AD severity, progression, and medication therapy impact.[4-10] In some studies, caregiver preferences are documented using the Alzheimer Disease Caregiver Preference Questionnaire (ADCPQ).[11, 12]

Table 1. Outcome Measures of Standard Tests Used in Evaluating AD Patients[4-8, 10]

Name of Test	Scale in Points	Efficacy Measures Assessed
Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)	0 to 70 Higher score reflects greater cognitive impairment	Attention, Comprehension , Memory, Orientation, and Reasoning
Alzheimer Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC)	1 to 7 1 = marked improvement 4 = no change 7 = marked worsening	Clinician impression of change in: Cognition, Behavior, Social functioning, and Daily functioning
Alzheimer Disease Cooperative Study-Activities of Daily Living (ADCS-ADL)	0 to 78 Higher score reflects better functioning	Ability to perform these activities of daily living: Personal care, Appliance use, Dressing activities, Toileting, and Bathing
Mini-Mental State Exam (MMSE)	0 to 30 0 = severe impairment 30 = normal	Attention, Calculation, Language, Memory, and Orientation
Neuropsychiatric Inventory (NPI)	0 to 120 Higher score reflects greater psychiatric disturbance	Severity and frequency of these psychiatric measures: Aberrant motor behavior, Agitation / aggression, Anxiety, Apathy, Delusions, Disinhibitions, Dysphoria, Euphoria, Hallucinations, and Irritability / lability
Trail Making Test A	Timed test (Shorter time represents better cognitive function)	Attention, Visual tracking, and Motor processing speed

Pharmacology

Rivastigmine is a reversible cholinesterase inhibitor which acts centrally to enhance cholinergic function.[1, 3] As a class, cholinesterase inhibitors increase the availability of the neurotransmitter acetylcholine. In theory, the increase in central acetylcholine concentration improves neuronal function in cholinergic pathways.[1] Members within this class vary greatly in chemical structure, target receptors and affinity for target receptors.[3] There are two main categories of cholinesterases found throughout the body: acetylcholinesterases (AChE) and butyrylcholinesterases (BChE).[3] Rivastigmine has a ten-fold greater affinity for brain AChE than for other peripheral forms of the enzyme. This is important as inhibition of peripheral AChE may increase adverse reactons.[3] Several forms of AChE have been identified. In the normal brain, the G4 isoform predominates and the G1 isoform is present in lesser amounts.[3] As AD progresses, G4 levels diminish and the predominant AChE is G1.[3, 13] Rivastigmine inhibits G1 six times more strongly than it inhibits G4.[3, 13] However, as AD progresses and fewer cholinergic neurons remain, the beneficial effects of rivastigmine may diminish.[1, 13] Rivastigmine also inhibits BChE, but less predictably.[3]

Pharmacokinetics

Rivastigmine is absorbed from the patch transdermally. Approximately 50% of the total drug contained in the matrix-type transdermal system is absorbed over 24 hours.[1] After an initial lag of 0.5-1 hours, plasma concentrations increase slowly.[1, 2] Peak plasma concentrations are achieved approximately 8 hours after patch application, but can vary per patient, sometimes being achieved after 10 to 16 hours following application.[1] Plasma concentrations gradually decrease over the balance of the application period. The extent of absorption is site-specific.[14] Application to the abdomen or thigh will result in 20-30% lower plasma concentrations of rivastigmine versus the chest, upper back or upper arm.[1] In addition to site-specific absorption, a relationship between body weight and steady-state concentration has been reported. A patient weighing 35 kg will have approximately double the steady-state concentration present in a 65 kg patient. At therapeutic concentrations, rivastigmine is approximately 40% protein-bound. The volume of distribution is 1.8 to 2.7 L/kg. Minimal metabolism occurs via the cytochrome P450 isoenzymes. Rivastigmine is metabolized via cholinesterase-mediated hydrolysis. Metabolites are excreted renally. Renal clearance is approximately 2.1 to 2.8 L/hr and the plasma elimination half-life is approximately 3 hours following patch removal.[1]

Absorption differences between the transdermal and oral formulations are of key interest. Total drug exposure to rivastigmine is comparable from the 9.5 mg/24 hours patch and the 6 mg twice daily oral capsule,[15] but is greater with the 9.5 mg/24 hours patch than with 3 mg oral solution.[16] However, plasma concentrations show less peak and trough variation with the transdermal formulation compared with either the capsule or the oral solution.[15, 16] Trials with oral rivastigmine have demonstrated gastrointestinal adverse effects are associated with high plasma concentrations of rivastigmine.[15, 17] The steadier delivery of rivastigmine and consequent improved tolerability was the rationale for development of a transdermal delivery system for rivastigmine.[15] Table 2 presents a pharmacokinetic comparison of rivastigmine transdermal and oral formulations.

Table 2. Pharmacokinetic Comparison of Transdermal and Oral Rivastigmine[1, 17, 18]

Pharmacokinetic Parameter	Transdermal 4.6 mg/24 hours	Transdermal 9.5 mg/24 hours	Oral capsule 3 mg twice daily	Oral capsule 6 mg twice daily
Peak serum concentration in ng/mL (SD)	2.7 (1.2)	7.9 (2.9)	9.7 (5.1)	29.3 (13.2)
Time to peak serum concentration (median)	8.0 hours	8.0 hours	1.0 hours	1.0 hours
Exposure as AUC_{24h} in (ng)(hr)/mL (SD)	46.3 (17.2)	127 (41.4)	57.7 (39.1)	191 (140)
Apparent elimination half-life	~ 3 hours after patch removal	~ 3 hours after patch removal	~ 1.5 hours	~ 1.5 hours
Fluctuation index[a] (SD)	0.6 (0.4)	0.8 (0.3)	4.0 (1.2)	4.2 (2.5)

Abbreviations: AUC = area under the curve; ng = nanogram; SD = standard deviation.
[a] Fluctuation index = (peak serum concentration – minimum serum concentration)/ average serum concentration.

Special Populations

Patients weighing 50 kg or less are more likely to suffer adverse effects such as nausea and vomiting when starting therapy or with upward dose titration than patients weighing greater than 50 kg. No dosage adjustments are necessary for age, or for hepatic or renal impairment. Titrate dose according to individual tolerability.[1]

In patients concomitantly using nicotine and rivastigmine oral formulation, the clearance of rivastigmine is increased by 23%. The effect of nicotine on the clearance of rivastigmine in patients using rivastigmine transdermal system has not been reported. Product labeling for rivastigmine transdermal states no dosage adjustment is necessary.[1]

Clinical Efficacy

A single phase III controlled-trial (IDEAL) evaluated rivastigmine transdermal system in patients with AD (n=1,195).[19, 20] In this trial, the transdermal formulation was compared to the oral rivastigmine formulation and to placebo. The effectiveness of the oral rivastigmine formulation has been established in two controlled-trials in AD and one controlled-trial in PD.[18, 21-23] No controlled clinical trials have studied the transdermal formulation for dementia of PD. Transdermal rivastigmine is labeled for dementia of PD based on bioequivalence with the oral formulation.[2]

The IDEAL (Investigation of transDermal Exelon in ALzheimer's disease) study is summarized in Table 3.[19, 20] Rivastigmine transdermal 9.5 mg/24 hours and 17.4 mg/24 hours strengths were compared to oral capsules and placebo. The duration of the trial was 24 weeks; however, this included a 16 week titration period in all treatment groups. Additionally, dosage adjustments and interruptions were allowed for tolerability at any time during the study. Primary outcomes were measured using the ADAS-Cog and ADCS-CGIC. Secondary outcome measures included the ADCS-ADL, MMSE, NPI, Ten Point Clock-drawing Test, and the Trail-making Test Part A. Assessments were performed at weeks 0, 16, and 24. The ADAS-Cog score improvements were statistically significant for all treatment groups compared to placebo ($p<0.05$). The efficacy of both patch strengths demonstrated non-inferiority to the oral capsule.

While the 9.5 mg/24 hour patch and the oral formulation were statistically better than placebo on the ADCS-CGIC evaluation, the 17.4 mg/24 hour patch failed to show superiority to placebo (intent-to-treat, last-observation-carried-forward). All treatment groups were statistically superior to placebo in ADCS-ADL, MMSE, and Trail-making Test Part A (all $p<0.05$). There was no significant difference in any treatment group compared with placebo on the Ten-point Clock-Drawing test or NPI assessments.[20] Adverse events in the trial were predominantly cholinergic-type reactions. The most frequent adverse events were nausea, vomiting and diarrhea. No significant differences in adverse event rates occurred between the 9.5 mg/24 hours patch and placebo. Rates of nausea and vomiting were approximately two-thirds lower in the 9.5 mg/24 hours patch group (6-7%) compared to the oral capsule group (17-23%). This tolerability advantage was lost at the 17.4 mg/24 hours dose, as rates of adverse events were comparable between the 17.4 mg/24 hours patch and oral capsule groups.[19] The 9.5 mg/24 hours patch delivered comparable efficacy to the maximum recommended rivastigmine oral dose of 12 mg/day with better gastrointestinal tolerability.[19, 20]

The overall clinical effectiveness of rivastigmine transdermal in dementia of AD, as with other members of its class, is modest.[24, 25] In the IDEAL study, a clinically meaningful improvement in the ADAS-Cog was defined as a decrease of at least 4 units at 24 weeks. Although the mean improvement for all treatment groups (-0.6 to -1.6 units) was statistically significant compared to placebo (1.0, $p<0.005$) no group reached the clinically meaningful 4-unit improvement. The percent of patients in each group who achieved a clinically meaningful decrease of at least 4 units from baseline were 27.4% for the 9.5 mg/24 hours patch, 32.8% for the 17.4 mg/24 hours patch, 28.5% for the 6 mg twice-daily capsule, and 19.9% for placebo ($p < 0.05$ all groups vs. placebo).[20]

Table 3. Clinical Trials of Rivastigmine Transdermal System vs. Rivastigmine Oral in Alzheimer Disease Patients

Reference/ Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes			Grade *
				Results	Response Rate	Discontinuation Rate	
Winblad B, et al, 2007[19, 20] The IDEAL study Experimental parallel: randomized, double-blind, placebo and active-controlled, multicenter	1,195	Patients aged 50-85 years with probable AD diagnosed according to NINCDS/ADRDA criteria, and having a MMSE score 10 to 20. Patients were required to have contact with a caregiver daily or reside with someone willing to supervise treatment.	Four groups: Rivastigmine patch 9.5 mg/24 hours (10 cm^2) once daily Mean dose = 9.8 cm^2 Rivastigmine patch 17.4 mg/24 hours (20 cm^2) once daily Mean dose = 16.5 cm^2 Rivastigmine capsules 12 mg/day (dose split and given twice daily) Mean dose = 9.7 mg/day Placebo Patients titrated to target dose during 16-week titration phase, then maintained at the highest tolerated dose within groups for 8-week maintenance phase Dosage adjustments and interruptions for tolerability were allowed Primary and secondary outcomes were measured with questionnaires	At week 24: ADAS-Cog scores • Rivastigmine all groups > placebo • Rivastigmine patch = rivastigmine oral ADAS-CGIC scores • Rivastigmine patch 9.5 mg/24 hours and rivastigmine oral > placebo • Rivastigmine patch 17.4 mg/24 hours = placebo	Mean (SD) change at week 24: **Primary Outcomes** • ADAS-Cog scores 10 cm^2: -0.6 (6.4), p = 0.005 20 cm^2: -1.6 (6.5), p<0.001 Capsule: -0.6 (6.2), p = 0.003 Placebo: 1.0 (6.8) • ADCS-CGIC scores 10 cm^2: 3.9 (1.2), p = 0.01 20 cm^2: 4.0 (1.3), NS Capsule: 3.9 (1.3), p = 0.009 Placebo: 4.2 (1.3) **Secondary outcomes** • ADCS-ADL scores 10 cm^2: -0.1 (9.1), p = 0.01 20 cm^2: 0.0 (11.6), p = 0.02 Capsule: -0.5 (9.5), p = 0.04 Placebo: -2.3 (9.4) • MMSE scores 10 cm^2: 1.1 (3.3), p = 0.002 20 cm^2: 0.9 (3.4), p<0.001 Capsule: 0.8 (3.2), p = 0.002 Placebo: 0.0 (3.5) • Trail Making Test A scores 10 cm^2: -12.3(55.1), p<0.001 20 cm^2: -6.5 (55.9), p = 0.005 Capsule: -9.8 (66.1), p<0.001 Placebo: 7.7 (56.6) Differences between active groups and placebo NS for: • Ten-point Clock-Drawing • NPI-12 scores • NPI distress scores	Rivastigmine 10 cm^2 64//293 (21.8%) 9.6% ADR 7.2% withdrew 1.4% death 1.0% lack of effect 1.6% other 1.0% lost to follow-up Rivastigmine 20 cm^2 62/303 (20.5%) 8.6% ADR 6.3% withdrew 1.7% death 1.3% lack of effect 1.4% other 1.3% lost to follow-up Rivastigmine capsule 63/297 (21.2%) 8.1% ADR 5.7% withdrew 0.7% death 2.7% lack of effect 2.3% other 1.7% lost to follow-up Placebo 36/302 (11.9%) 5.0% ADR 2.0% withdrew 1.0% death 2.0% lack of effect 1.0% other 1.0% lost to follow-up	1

Abbreviations: AD = Alzheimer's disease; ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living scale; ADCS-CGIC = Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; ADR = Adverse events; MMSE = Mini-Mental State Examination; N = number of patients enrolled in trial or specific treatment group; NINCDS/ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NPI = Neuropsychiatric Inventory; NS = no significance; SD = standard deviation

* Grade of Scientific Evidence. Refer to Appendix for definitions.

Adverse Drug Reactions

The most common adverse drug reactions reported in the single controlled clinical trial were nausea, vomiting, and diarrhea.[1] Nausea and vomiting were cited as the adverse effects most commonly leading to discontinuation of treatment. Overall discontinuation rates and rates due to nausea and vomiting are presented in Table 4. Table 5 presents the adverse drug reactions as reported in product labeling, including comparison to oral capsules and placebo.[1]

Table 4. Discontinuation Rates as Presented in Product Labeling[1]

Cause of Discontinuation	Rivastigmine Patch 9.5 mg/24 hr	Rivastigmine Patch 17.4 mg/24 hr	Rivastigmine Capsule 6 mg BID	Placebo
Any adverse event	9.6%	8.6%	8.1%	5.0%
Nausea	0.7%	1.7%	1.7%	1.3%
Vomiting	0%	1.7%	2.0%	0.3%

Abbreviations: BID = twice daily; hr = hours.

Table 5. Patients (%) with Adverse Drug Reactions with a Frequency ≥ 2% and at a Rate Exceeding Placebo[1]

Adverse Event	Rivastigmine Patch 9.5 mg/24 hr n = 291	Rivastigmine Patch 17.4 mg/24 hr n = 303	Rivastigmine Capsule 6 mg BID n = 294	Placebo n = 302
Gastrointestinal				
Abdominal pain	2	4	1	1
Diarrhea	6	10	5	3
Nausea	7	21	23	5
Vomiting	6	19	17	3
Central and Peripheral Nervous System				
Anxiety	3	3	2	1
Depression	4	4	4	1
Dizziness	2	7	7	2
Fatigue	2	2	1	1
Headache	3	4	6	2
Insomnia	1	4	2	2
Vertigo	0	2	1	1
Miscellaneous				
Asthenia	2	3	6	1
Loss of appetite	3	9	9	2
Upper abdominal pain	1	3	2	2
Urinary tract infection	2	2	1	1
Weight loss	3	8	5	1

Abbreviations: BID = twice daily; hr = hours.

Drug Interactions

Rivastigmine has not been evaluated for specific interactions. Rivastigmine is primarily metabolized through esterase hydrolysis, and is minimally metabolized via CYP450 isoenzymes.[1] Inducers or inhibitors of CYP450 metabolism are not expected to affect the metabolism of rivastigmine. Do not use rivastigmine concomitantly with other cholinesterase

inhibitors or cholinomimetic medications. Rivastigmine may diminish the efficacy of anticholinergic medications. Rivastigmine may increase the effects of depolarizing neuromuscular blocking agents such as succinylcholine or cholinergic agents such as bethanechol.[1, 26]

Dosage and Administration

Rivastigmine transdermal system is available in two patch sizes: 4.6 mg/24 hours (5 cm^2) and 9.5 mg/24 hours (10 cm^2).[1] The starting dose of rivastigmine transdermal system is 4.6 mg/24 hours applied once daily. After four weeks the dose may be titrated upward to 9.5 mg/24 hours if the initial dose is well tolerated. The recommended effective dose is 9.5 mg/24 hours. If intolerable gastrointestinal adverse effects occur, discontinue patch application for several days. Resume treatment at the same or at a lower dose. Treatment which is interrupted for longer than several days must be reinitiated at the 4.6 mg/24 hours dose and titrated upward after four weeks as tolerated. The recommended maximum dose is 9.5 mg/24 hours.[1]

Patients may be switched from rivastigmine oral capsules or solution to rivastigmine transdermal. Initial patch size is 4.6 mg/24 hours for a patient taking less than 6 mg total daily dose of rivastigmine oral. A patient receiving a total oral daily dose of 6 to 12 mg may begin with the 9.5 mg/24 hours patch. Patch application is started the day after the last oral dose.[1]

Rivastigmine patch is applied once daily. The application site should be hairless, clean, dry and without irritation. Apply to the upper or lower back, or to the chest or upper arm if the back is not accessible. It is recommended to change the spot of application daily, and not to use the same spot twice within 14 days.[1]

Monitoring

The National Institute for Clinical Excellence (NICE) guidelines recommend monitoring AD patients on cholinesterase inhibitors for therapeutic efficacy every 6 months using MMSE and global, functional and behavioral assessment tests.[27] Monitor AD and PD patients for occurrences of adverse effects and make dose adjustments as appropriate. Monitor patients for weight loss which may be associated with gastrointestinal effects. Monitor PD patients for worsening of extrapyramidal symptoms, most notably tremor.[1]

Critical Issues

- Rivastigmine transdermal system is the first patch available for use in treatment of dementia of AD and PD, allowing once-daily dosing and convenient administration.
- In a single controlled-trial, rivastigmine transdermal demonstrated statistically significant improvement over placebo; however, clinical improvement was modest.
- Rivastigmine transdermal 9.5 mg/24 hours demonstrated comparable efficacy to the maximum recommended oral dose of rivastigmine and demonstrated better gastrointestinal tolerability.

Summary

Rivastigmine transdermal system offers a once-a-day therapeutic alternative to oral cholinesterase inhibitors in the treatment of dementia of AD. Rivastigmine oral and transdermal are the only agents labeled for use in dementia of PD. The benefits of rivastigmine transdermal, as well as other members of its drug class, are modest. The adverse effects of this agent in AD patients are generally mild to moderate and include nausea, vomiting, and diarrhea. Adverse effects may impact dose titration schedule and overall patient tolerability. Rivastigmine transdermal has not been compared in clinical trials to oral cholinesterase agents other than rivastigmine oral for efficacy and safety in AD and PD patients.

References

1. Novartis. Exelon patch (rivastigmine transdermal system) product information. Bridgewater, NJ: Novartis Pharmaceuticals; 2009.
2. United BioSource Corporation. Submission of Clinical and Economic Data Supporting Formulary Consideration of Exelon Patch (rivastigmine transdermal system). Bethesda, MD: United BioSource Corporation; 2007.
3. Krall WJ, Sramek JJ, Cutler NR. Cholinesterase inhibitors: a therapeutic strategy for Alzheimer disease. *Ann Pharmacother.* Apr 1999;33(4):441-450.
4. Rosen WG, Mohs RC, Davis KL. A New Rating Scale for Alzheimer's Disease. *Am J Psychiatry.* Nov 1984;141:1356-1364.
5. Schneider LS, Olin JT, Doody RS, et al. Validity and Reliability of the Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change. *Alzheimer Dis Assoc Discord.* 1997;11(Suppl 2):S22-S32.
6. Galasko D, Bennett D, Sano M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Discord.* 1997;11(Suppl 2):S33-S39.
7. Flostein MF, Flostein SE, McHugh PR. Mini-Mental State: A Practical Method for Grading the Cognitive State of Patients for the Clinician. *J Psychiatr Res.* Nov 1975;12(3):189-198.
8. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology.* Dec 1994;44(12):2308-2314.
9. Watson YI, Arfken CL, Brige SJ. Clock completion: an objective screening test for dementia. *J Am Geriatr Soc.* Nov 1993;41(11):1235-1240.
10. Buck KK, Atkinson TM, Ryan JP. Evidence of practice effects in variants of the Trail Making Test during serial assessment. *Journal of Clinical and Experimental Neuropsychology.* 2007:1-7.
11. Blesa R, Ballard C, Orgogozo JM, Lane R, Thomas SK. Caregiver preference for rivastigmine patches versus capsules for the treatment of Alzheimer disease. *Neurology.* Jul 24 2007;69(4 Suppl 1):S23-28.
12. Winblad B, Kawata AK, Beusterien KM, et al. Caregiver preference for rivastigmine patch relative to capsules for treatment of probable Alzheimer's disease. *Int J Geriatr Psychiatry.* May 2007;22(5):485-491.
13. Faulkner JD, Bartlett J, Hicks P. Chapter 63: Alzheimer's disease. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy. A*

Pathophysiologic Approach. 6th ed. New York, NY: McGraw-Hill Medical Publishing Division; 2005:1157-1173.

14. Lefevre G, Sedek G, Huang HL, et al. Pharmacokinetics of a rivastigmine transdermal patch formulation in healthy volunteers: relative effects of body site application. *J Clin Pharmacol.* Apr 2007;47(4):471-478.
15. Cummings J, Lefevre G, Small G, Appel-Dingemanse S. Pharmacokinetic rationale for the rivastigmine patch. *Neurology.* Jul 24 2007;69(4 Suppl 1):S10-13.
16. Lefevre G, Pommier F, Sedek G, et al. Pharmacokinetics and bioavailability of the novel rivastigmine transdermal patch versus rivastigmine oral solution in healthy elderly subjects. *J Clin Pharmacol.* Feb 2008;48(2):246-252.
17. Lefevre G, Sedek G, Jhee SS, et al. Pharmacokinetics and Pharmacodynamics of the Novel Daily Rivastigmine Transdermal Patch Compared With Twice-daily Capsules in Alzheimer's Disease Patients. *Clin Pharmacol Ther.* May 23 2007.
18. Novartis. Exelon (rivastigmine tartrate) Capsules and Oral Solution product information. East Hanover, NJ: Novartis Pharmaceuticals; 2006.
19. Winblad B, Grossberg G, Frolich L, et al. IDEAL: a 6-month, double-blind, placebo-controlled study of the first skin patch for Alzheimer disease. *Neurology.* Jul 24 2007;69(4 Suppl 1):S14-22.
20. Winblad B, Cummings J, Andreasen N, et al. A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease--rivastigmine patch versus capsule. *Int J Geriatr Psychiatry.* May 2007;22(5):456-467.
21. Rosler M, Anand R, Cicin-Sain A, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. *Bmj.* Mar 6 1999;318(7184):633-638.
22. Corey-Bloom J, Anand R, Veach J. A randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. *International Journal of Geriatric Psychopharmacology.* 1998;1:55-65.
23. Emre M, Aarsland D, Albanese A, et al. Rivastigmine for dementia associated with Parkinson's disease. *N Engl J Med.* Dec 9 2004;351(24):2509-2518.
24. Doody RS, Stevens JC, Beck C, et al. Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* May 8 2001;56(9):1154-1166.
25. Waldemar G, Dubois B, Emre M, et al. Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. *Eur J Neurol.* Jan 2007;14(1):e1-26.
26. Baxter K, ed. *Stockley's Drug Interactions.* 8th ed. Grayslake, IL: Pharmaceutical Press; 2008.
27. Dillon A. Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease (amended). NICE technology appraisal guidance 111 (amended). Available online at http://www.nice.org.uk/nicemedia/pdf/word/TA111Alzheimer'sfinalguidanceamendedSep07.doc (accessed on January 7, 2008). Updated November 2006 (amended September, 2007). London, UK: National Institute for Health and Clinical Excellence; 2006.

Document Information

Prepared by: Joanne C. Chapman, PharmD Student and Ginny Jones, RPh, Drug Information Specialist
Edited by: Linda S. Tyler, PharmD, Administrative Director, Pharmacy Services, and M. Christina Beckwith, PharmD, Drug Information Specialist
Date: March 2, 2009
©2009 University of Utah, Drug Information Services, Salt Lake City, UT.

Appendix: Grades of Scientific Evidence

Grade 1. Evidence from randomized, blinded, placebo-controlled, clinical trials in peer reviewed journals
Grade 2. Non-randomized controlled trials
Grade 3. Non-randomized historical cohort studies. Other studies with non-experimental designs (eg, population based studies, case-control studies)
Grade 4. Case reports, case series, abstracts of trials
Grade 5. Consensus of experts where data are incomplete or inconsistent