Transdermal rivastigmine for dementia

Carl Sadowsky, MD

The rivastigmine patch is the first transdermal treatment for symptoms of mild to moderate Alzheimer’s disease (AD) and mild to moderate Parkinson’s disease dementia (Table). Rivastigmine, a cholinesterase inhibitor, is the only therapy approved for both indications.1

Clinical implications

The rivastigmine patch offers continuous drug delivery through the skin into the bloodstream over 24 hours.1 This may reduce the incidence of side effects compared with oral rivastigmine,2 making optimal therapeutic doses easier to attain.3 The target dose 9.5 mg/24 hours patch provides efficacy similar to the highest recommended rivastigmine capsule dose (6 mg bid for a total of 12 mg/d).3

How it works

The rivastigmine patch uses matrix technology, which enables delivery of a large amount of drug from a small surface area.4 The patch is available in 2 dosage forms:

• a 5-cm² size containing 9 mg of rivastigmine that delivers 4.6 mg/24 hours
• a 10-cm² size containing 18 mg of rivastigmine that delivers 9.5 mg/24 hours.

Each patch consists of 4 layers: the backing layer, an acrylic drug matrix, a silicone adhesive matrix, and an overlapping release liner that is removed and discarded before the patch is applied.1 Cholinesterase inhibitors are believed to exert their effects by increasing available levels of the neurotransmitter acetylcholine in the brain. Two studies have demonstrated that cognitive improvements associated with rivastigmine treatment correlate significantly with cholinesterase inhibition.5,6 In 1 study, rivastigmine’s inhibitory effects on cholinesterase were sustained for 12 months.6

Pharmacokinetics

Rivastigmine is metabolized by its target cholinesterase enzymes to the decarboxylation products 11:18:21

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Table

Rivastigmine transdermal patch: Fast facts

<table>
<thead>
<tr>
<th>Brand name: Exelon Patch</th>
<th>Class: Cholinesterase inhibitor</th>
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<tbody>
<tr>
<td>Indication: Symptomatic treatment of mild to moderate Alzheimer’s-type dementia and mild to moderate dementia associated with Parkinson’s disease</td>
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<td>Manufacturer: Novartis Pharmaceuticals, Inc.</td>
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<td>Dosing forms: 4.6 and 9.5 mg/24 hours transdermal patches (5 cm² and 10 cm², respectively)</td>
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<td>Recommended dosage: Start with 4.6 mg/24 hours patch for 24 weeks, followed by a one-step increase to the target dose 9.5 mg/24 hours patch</td>
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*Unless the patient is taking oral rivastigmine (see ‘Transitioning to rivastigmine patch,’ page 76)
Efficacy of transdermal rivastigmine for Alzheimer’s symptoms

In a 24-week study, transdermal rivastigmine, 9.5 mg/24 hours, and the highest recommended dose of oral rivastigmine (6 mg bid) showed comparable efficacy as measured by mean change in score on scales commonly used in Alzheimer’s disease clinical trials. ADAS-Cog assesses orientation, memory, language, praxis, and visuospatial functions. ADCS-CGIC provides a single global rating of change from baseline based on interviews with the patient and caregiver.

Rivastigmine has a half-life of 1 to 2 hours, so it is rapidly cleared. In the event of a serious reaction, significant clearance of rivastigmine from the body would occur within 3 hours of patch removal.

Centrally mediated cholinergic gastrointestinal (GI) side effects associated with oral rivastigmine are related to high maximum plasma concentrations (C_max) and short time interval to C_max (T_max). In an open-label, parallel-group study of 51 AD patients that compared rivastigmine patches with rivastigmine capsules, transdermal administration was associated with slower increases to lower peak plasma concentrations (prolonged T_max and reduced C_max), and less fluctuation in plasma concentration. Despite these effects, the rivastigmine 9.5 mg/24 hours patch provided drug exposure comparable to the highest dose of capsules (6 mg bid for a total of 12 mg/d), with improved GI tolerability.

Clinical Point
The 9.5 mg/24 hours patch provides drug exposure comparable to the highest dose of capsules (6 mg bid) with improved GI tolerability.
• 9.5 mg/24 hours rivastigmine patch
  (10-cm² patch; n=293)
• 6 mg bid rivastigmine capsules
  (n=297)
• or placebo (n=302).

Data for the 17.4 mg/24 hours patch are
not discussed here because this dose ex-
ceeds the FDA-approved maximum dosage
(9.5 mg/24 hours) and is not available.

Patients in the 9.5 mg/24 hours patch
group received a 4.6 mg/24 hours patch (5
cm²) for weeks 1 through 4, and then the
9.5 mg/24 hours patch for the remainder
of the study. Patients in the capsule group
started on 3 mg/d (1.5 mg bid) and were
titrated every 4 weeks in steps of 3 mg/d
to a maximum of 12 mg/d administered as
6 mg bid.

Primary outcomes were measured
as mean change in score from baseline
to endpoint on the Alzheimer’s Disease
Assessment Scale–Cognitive Subscale
(ADAS-Cog) and Alzheimer’s Disease Co-
operative Study–Clinical Global Impres-
sion of Change (ADCS-CGIC). By study
endpoint, the 9.5 mg/24 hours patch and
capsules, 12 mg/d, showed comparable
efficacy (Figure, page 73).² Compared with
those receiving placebo, patients in the 9.5
mg/24 hours patch and capsule groups
showed significant improvements in de-
mentia symptoms, including:
• cognition
• global performance
• attention
• activities of daily living.²

Based on my clinical experience, these
improvements reflect small but clinically
meaningful changes that are noted by pa-
tients and caregivers.

Safety and tolerability
Adverse events associated with rivastig-
mine are predominantly cholinergic; GI
side effects—nausea, vomiting, and diar-
rhea—are observed most frequently.² These
events occur less frequently with the patch
than with capsules. In the efficacy trial, pa-
tients in the 9.5 mg/24 hours rivastigmine
patch group had one-third as many reports
of nausea (7.2% vs 23.1%) and vomiting
(6.2% vs 17.0%) compared with the 6 mg bid
capsule group.²

Diarrhea was reported by 6% of subjects
receiving the 9.5 mg/24 hours patch, 5% of
those taking 6-mg capsule bid, and 3% re-
ceiving placebo. Fewer subjects in the 9.5
mg/24 hours patch group (3%) experienced
decreased weight compared with those
in the capsule group (5%). The rate of de-
creased weight with placebo was 1%.

Dizziness affected 2% of those in the 9.5
mg/24 hours patch and placebo groups;
incidence in the capsule group was signifi-
cantly higher at 8%. Headache was similar
with the 9.5 mg/24 hours patch (3%) and
placebo (2%), with the capsule significantly
higher at 6%.²

The proportion of patients who expe-
rienced no, slight, or mild skin irritation
ranged from 90% to 98%.² The most com-
monly reported moderate or severe skin ir-
ritations were erythema (8% rivastigmine
patch vs 4% placebo) and pruritus (7% riv-
astigmine patch vs 3% placebo). Two per-
cent of patients using active patch discon-
tinued the trial because of skin irritation.

Rivastigmine appears not to produce ad-
verse effects on cardiac function as assessed
by ECG. In clinical trials of 2,791 patients,
pooled 12-lead ECG data comparing oral
rivastigmine and placebo groups did not
differ significantly in heart rate or PR, QRS,
and QTc intervals.³

Dosing
The rivastigmine patch is administered
once daily, and the recommended mainte-
nance dose is the 9.5 mg/24 hours patch.
Start patients on a 4.6 mg/24 hours patch
for at least 4 weeks and then increase to the
9.5 mg/24 hours target dose if the lower
dose is well tolerated.

Dosage adjustment of rivastigmine is
not necessary in patients with hepatic or
renal disease because of minimal liver
metabolism and the acetylcholinesterase-
mediated hydrolysis of rivastigmine to the
inactive decarbamylated metabolite NAP
226-90, which is excreted in the urine.³³

continued from page 73

Clinical Point
The most common side effects of the
rivastigmine patch
are nausea (7.2%),
vomiting (6.2%), and
diarrhea (6%); severe
skin reactions are
relatively rare
Related Resource


Drug brand names

Digoxin - Lanoxin
Rivastigmine - Exelon

Disclosure

Dr. Sadowsky is a consultant to and speaker for Forest Pharmaceuticals and Novartis Pharmaceuticals.

Acknowledgment

The author thanks Christina Mackins, PhD, a medical writer for Alpha-Plus Medical Communications Ltd, for her editorial assistance with this article. Funding for her work was provided by Novartis Pharmaceuticals.

Clinical Point

Start most patients on the 4.6 mg/24 hours patch for ≥4 weeks and increase to the 9.5 mg/24 hours patch if the lower dose is well tolerated.

Transitoning to rivastigmine patch

The efficacy study included an open-label extension, during which blinding was maintained. This provided information on patients beginning rivastigmine patch therapy directly from placebo or transitioning from rivastigmine capsules to the target dose 9.5 mg/24 hours patch. Based on these results, transition patients as follows:

- Patients taking oral rivastigmine, <6 mg/d: Switch to a 4.6 mg/24 hours patch for 24 weeks before increasing to a 9.5 mg/24 hours patch.
- Patients taking oral rivastigmine, 6 to 12 mg/d: Switch directly to a 9.5 mg/24 hours patch.

Apply the first patch the day after the last oral dose.

References


Bottom Line

The 9.5 mg/24 hours rivastigmine patch is comparable to the highest recommended dose of oral rivastigmine (6 mg bid) in improving cognition and global performance. Compared with those taking 6-mg capsules bid, patients using the 9.5 mg/24 hours patch had approximately one-third as many reports of nausea (7.2% vs 23.1%) and vomiting (6.2% vs 17.0%).