

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**22-083**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use the Exelon® Patch safely and effectively. See full prescribing information for the Exelon Patch.

### Exelon® Patch (rivastigmine transdermal system)

Initial U.S. Approval: April 21, 2000

#### INDICATIONS AND USAGE

Exelon Patch contains rivastigmine, an acetylcholinesterase inhibitor indicated for the:

- Treatment of mild to moderate dementia of the Alzheimer's type (1.1)
- Treatment of mild to moderate dementia associated with Parkinson's disease (1.2)

#### DOSAGE AND ADMINISTRATION

Initial Dose	one Exelon Patch 4.6 mg/24 hours once daily (2.1)
Maintenance Dose	one Exelon Patch 9.5 mg/24 hours once daily (2.1)

A minimum of 4 weeks of treatment and good tolerability with the previous dose should be observed before increasing the dose (2.1).

#### DOSAGE FORMS AND STRENGTHS

Exelon Patch is a transdermal system.

**Exelon Patch 4.6 mg/24 hours:** 5 cm<sup>2</sup> size containing 9 mg rivastigmine

**Exelon Patch 9.5 mg/24 hours:** 10 cm<sup>2</sup> size containing 18 mg rivastigmine (3)

#### CONTRAINDICATIONS

Exelon Patch (rivastigmine transdermal system) is contraindicated in patients with known hypersensitivity to rivastigmine, other carbamate derivatives or other components of the formulation (4.1).

#### WARNINGS AND PRECAUTIONS

- Gastrointestinal adverse effects including nausea and vomiting can be significant and at times severe at higher than the recommended dose. The

dose should be titrated as prescribed and reinitiated at the lowest dose if interrupted for more than a few days (5.1).

- Weight should be monitored during the Exelon Patch therapy (5.1).
- As with other cholinomimetics, caution is recommended in patients with sick sinus syndrome, conduction defects (sino-atrial block, atrio-ventricular block), gastroduodenal ulcerative conditions (including those predisposed to such conditions by concomitant medications), asthma or chronic obstructive pulmonary disease, urinary obstruction, and seizures (5.5).
- Extrapyramidal symptoms may appear or be exacerbated (particularly tremor) (5.5).

#### ADVERSE REACTIONS

The most commonly observed adverse events occurring at a frequency of at least 5% and at a frequency at least greater than placebo with administration of 9.5 mg/24 hours were nausea, vomiting and diarrhea. Other less common and sometimes serious adverse events have been reported (6).

To report SUSPECTED ADVERSE REACTIONS, contact NOVARTIS PHARMACEUTICALS CORPORATION at 1-888-NOW-NOVA or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

Other cholinomimetic drugs, anticholinergic medications, succinylcholine-type muscle relaxants during anesthesia (7).

#### USE IN SPECIFIC POPULATIONS

Caution is advised in patients with body weight below 50 kg (2.1, 5.12, 8.8). The safety of the Exelon Patch is not established in pregnant and lactating women (8.2). Not recommended for use in children (5.12).

### See 17 for PATIENT COUNSELING INFORMATION

Initial Issue

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Alzheimer's Disease

Exelon Patch (rivastigmine transdermal system) is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

#### 1.2 Parkinson's Disease Dementia

Exelon Patch (rivastigmine transdermal system) is indicated for the treatment of mild to moderate dementia associated with Parkinson's disease.

The dementia of Parkinson's disease is purportedly characterized by impairments in executive function, memory retrieval, and attention, in patients with an established diagnosis of Parkinson's disease. The diagnosis of the dementia of Parkinson's disease can be made reliably in patients in whom a progressive dementia syndrome occurs (without the necessity to document the specific deficits described above) at least 2 years after a diagnosis of Parkinson's disease has been made, and in whom other causes of dementia have been ruled out.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Alzheimer's Disease

Table 1 Patch Size, Drug Content And Nominal Delivery Rate

Rivastigmine Nominal Dose	Rivastigmine Content per Exelon Patch	Exelon Patch Size
4.6 mg/24 hours	9 mg	5 cm <sup>2</sup>
9.5 mg/24 hours	18 mg	10 cm <sup>2</sup>

**Initial Dose:** Treatment is started with the Exelon Patch 4.6 mg/24 hours.

After a minimum of four weeks of treatment and if well tolerated, this dose should be increased to Exelon Patch 9.5 mg/24 hours, which is the recommended effective dose.

**Maintenance Dose:** Dose increases should occur only after a minimum of 4 weeks at the previous dose, and only if the previous dose has been well tolerated. The maximum recommended dose is 9.5 mg/24 hours. Higher doses confer no appreciable additional benefit, and are associated with significant increase in the incidence of adverse events (see *Adverse Reactions (6)*).

If adverse effects (e.g., nausea, vomiting, diarrhea, loss of appetite) cause intolerance during treatment, the patient should be instructed to discontinue treatment for several days and then restart at the same or next lower dose level. If treatment is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose and titrated as described above (also see *Warnings and Precautions (5)*).

#### **Switching from Capsules or Oral Solution:**

Patients treated with Exelon capsules or oral solution may be switched to Exelon Patches as follows:

A patient who is on a total daily dose of <6 mg of oral rivastigmine can be switched to Exelon Patch 4.6 mg/24 hours.

A patient who is on a total daily dose of 6 to 12 mg of oral rivastigmine may be directly switched to Exelon Patch 9.5 mg/24 hours.

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

#### Method of Administration

Exelon patches should be applied once a day to clean, dry, hairless, intact healthy skin in a place that will not be rubbed against by tight clothing. The upper or lower back is recommended as the site of application because the patch is less likely to be removed by the patient; however, when sites on the back are not accessible the patch can be applied to the upper arm or chest. The patch should not be applied to skin that is red, irritated, or cut. It is recommended that the site of patch application be changed 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 same site should not be used within 14 days.

The patch should be pressed down firmly until the edges stick well. The patch can be used in situations that include bathing and hot weather.

The patch should be replaced with a new one every 24 hours. Patients and caregivers should be instructed accordingly (See *Patient Counseling Information (17)*).

#### Incompatibilities

To prevent interference with the adhesive properties of the patch, the patch should not be applied to a skin area where cream, lotion or powder has recently been applied.

#### Special Populations

**Hepatic Impairment:** Dosage adjustment is not necessary in hepatically impaired patients, as the dose of drug is individually titrated to tolerability.

**Renal Impairment:** No dose adjustment is necessary for patients with renal impairment.

**Low Body Weight:** Patients with body weight below 50 kg may experience more adverse events and may be more likely to discontinue due to adverse events. Particular caution should be exercised in titrating these patients above the recommended maintenance dose of Exelon Patch 9.5 mg/24 hours.

#### 2.2 Parkinson's Disease Dementia

See *Dosage and Administration (2.1)*.

### 3 DOSAGE FORMS AND STRENGTHS

#### 3.1 Dosage Form

Patch.

Each patch is a thin, matrix-type transdermal system consisting of three layers when worn by the patient. A fourth layer, the release liner, covers the adhesive layer prior to use and is removed at the time the system is applied to the skin.

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

- "Exelon® Patch "4.6 mg/24 hours" and "AMCX"
- "Exelon® Patch "9.5 mg/24 hours" and "BHD1"

#### 3.2 Dosage Strengths

Table 1 summarizes the available strengths and quantity of rivastigmine provided in each patch:

- Each 5 cm<sup>2</sup> patch contains 9 mg rivastigmine base, with *in vivo* release rate of 4.6 mg/24 hours.
- Each 10 cm<sup>2</sup> patch contains 18 mg rivastigmine base, with *in vivo* release rate of 9.5 mg/24 hours.

For a full list of excipients, see *Description (11)*.

## 4 CONTRAINDICATIONS

### 4.1 Hypersensitivity

Exelon Patch (rivastigmine transdermal system) is contraindicated in patients with known hypersensitivity to rivastigmine, other carbamate derivatives, or other components of the formulation (see *Description (11)*).

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Gastrointestinal Adverse Reactions

**At higher than recommended doses Exelon Patch (rivastigmine transdermal system) use is associated with significant gastrointestinal adverse reactions, including nausea, vomiting, diarrhea, anorexia/decreased appetite and weight loss. For this reason, patients administered the Exelon Patch should always be started at a dose of 4.6 mg/24 hours and titrated to the maintenance dose of 9.5mg/24 hours. If treatment is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose (see *Dosage and Administration (2)*) to reduce the possibility of severe vomiting and its potentially serious sequelae (e.g., there has been one post-marketing report of severe vomiting with esophageal rupture following inappropriate reinitiation of treatment with a 4.5-mg dose of an oral formulation after 8 weeks of treatment interruption).**

**At higher than recommended doses caregivers should be advised of the high incidence of nausea and vomiting associated with the use of the Exelon Patch along with the possibility of anorexia and weight loss. Caregivers should be encouraged to monitor for these adverse events and inform the physician if they occur. It is critical to inform caregivers that if therapy has been interrupted for more than several days, the next dose should not be administered until they have discussed this with the physician.**

***Nausea and Vomiting:*** In the controlled clinical trial, 7% of patients treated with the Exelon Patch 9.5mg/24 hours developed nausea, as compared to 23% of patients who received the Exelon capsule at doses up to 6 mg BID and 5% of those who received placebo. In the same clinical trial, 6% of patients treated with Exelon Patch 9.5mg/24 hours developed vomiting, as compared with 17% of patients who received the Exelon capsule at doses up to 6 mg BID and 3% of those who received placebo. The proportion of patients who discontinued treatment due to vomiting was 0% of the patients who received the Exelon Patch 9.5mg/24 hours as well as 2% of patients who received the Exelon capsule at doses up to 6 mg BID and 0% of those who received placebo. Vomiting was severe in 0% of patients who received the Exelon Patch 9.5mg/24 hours and 1% of patients who received the Exelon capsule at doses up to 6 mg BID and 0% of those who received placebo.

In the same clinical trial 21% of the patients treated with the higher dose of Exelon Patch 17.4 mg/24 hours developed nausea, 19% developed vomiting, and the proportion of these patients who discontinued treatment due to vomiting was 2%. Vomiting was severe in 1% of the patients treated with the Exelon Patch 17.4 mg/24.

***Weight Loss:*** In the controlled clinical trial, the proportion of patients who had weight loss equal to or greater than 7% of their baseline weight was 8% of those treated with the Exelon Patch 9.5 mg/24 hours, 11% of patients who received the Exelon capsule at doses up to 6 mg BID and 6% of those who received placebo.

In the same clinical trial, 12% of those treated with 17.4mg/24 hours had weight loss equal to or greater than 7% of their baseline weight. It is not clear how much of the weight loss was associated with anorexia, nausea, vomiting, and the diarrhea associated with the drug.

***Diarrhea:*** In the controlled clinical trial, 6% of the patients treated with the Exelon Patch 9.5 mg/24 hours developed diarrhea, as compared with 5% of patients who received the Exelon capsule at doses up to 6 mg BID, 10% of those treated with 17.4mg/24 hours and 3% of those who received placebo.

***Anorexia/Decreased Appetite:*** In the controlled clinical trial, 3% of the patients treated with the Exelon Patch 9.5 mg/24 hours were recorded as developing decreased appetite or anorexia, as compared with 9% of patients who received the Exelon capsule at doses up to 6 mg BID, 9% of those treated with Exelon Patch 17.4mg/24 hours and 2% of those who received placebo.

***Peptic Ulcers/Gastrointestinal Bleeding:*** Because of their pharmacological action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal antiinflammatory drugs (NSAIDs). Clinical studies of Exelon have shown no significant increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

### 5.2 Anesthesia

Exelon, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

### 5.3 Cardiovascular Conditions

Drugs that increase cholinergic activity may have vagotonic effects on heart rate (e.g., bradycardia). The potential for this action may be particularly important to patients with sick sinus syndrome or other supraventricular cardiac conduction conditions. In clinical trials, Exelon was not associated with any increased incidence of cardiovascular adverse events, heart rate or blood pressure changes, or ECG abnormalities.

### 5.4 Genitourinary Conditions

Although this was not observed in clinical trials of Exelon, drugs that increase cholinergic activity may cause urinary obstruction.

### 5.5 Neurological Conditions

***Seizures:*** Drugs that increase cholinergic activity are believed to have some potential for causing seizures. However, seizure activity also may be a manifestation of Alzheimer's disease.

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

### 5.6 Pulmonary Conditions

Like other drugs that increase cholinergic activity, Exelon should be used with care in patients with a history of asthma or obstructive pulmonary disease.

### 5.7 Effects on Ability to Drive and Use Machines

Dementia may cause gradual impairment of driving performance or compromise the ability to use machinery. The administration of rivastigmine may also result in adverse events that are detrimental to these functions. Thus, the ability to continue driving or operate machinery should be routinely evaluated by the treating physician.

### 5.8 Special Populations

***Low Body Weight:*** Patients with body weight below 50 kg may experience more adverse events and may be more likely to discontinue due to adverse events. Particular caution should be exercised in titrating these patients above the recommended maintenance dose of the Exelon Patch 9.5 mg/24 hours.

## 6 ADVERSE REACTIONS

Significant gastrointestinal adverse reactions including nausea vomiting, anorexia, and weight loss have been reported with the Exelon Patch at higher than recommended doses (See *Warnings and Precautions* (5.1)).

### 6.1 Incidence in controlled clinical trial in Alzheimer's Disease

**Associated with discontinuation of treatment:** In the single controlled clinical trial of the Exelon Patch (see *Clinical Studies* (14)), which randomized a total of 1195 patients, the proportions of patients in the Exelon Patch 9.5 mg/24 hours, the Exelon Patch 17.4 mg/24 hours, Exelon capsules 6 mg BID, and placebo groups who discontinued treatment due to adverse events were 9.6%, 8.6%, 8.1%, and 5.0%, respectively.

The most common adverse events in the Exelon Patch-treated groups that led to treatment discontinuation in this study were nausea and vomiting. The proportions of patients who discontinued treatment due to nausea were 0.7%, 1.7%, 1.7%, and 1.3% in the Exelon Patch 9.5 mg/24 hours, Exelon Patch 17.4 mg/24 hours, the Exelon capsules 6 mg BID, and placebo groups, respectively. The proportions of patients who discontinued treatment due to vomiting were 0%, 1.7%, 2.0%, and 0.3% in the Exelon Patch 9.5 mg/24 hours, the Exelon Patch 17.4 mg/24 hours, Exelon capsules 6 mg BID, and placebo groups, respectively.

**Most commonly observed adverse events:** The most commonly observed adverse events seen in patients administered the Exelon Patch in the controlled clinical trial, defined as those occurring at a frequency of at least 5% in the 9.5 mg/24h group and at a frequency at least as high as in the placebo group are largely predicted by Exelon's cholinergic effects. These are nausea, vomiting, and diarrhea. All these events were more common at the higher Exelon Patch dose of 17.4 mg/24 hours than at a dose of 9.5 mg/24 hours.

**Adverse events observed at an incidence of  $\geq$  2%:** The following table lists treatment-emergent adverse events that were seen at an incidence of  $\geq$  2% in either Exelon Patch-treated group in the controlled clinical trial and for which the rate of occurrence was greater for patients treated with that dose of the Exelon Patch than for those treated with placebo. The prescriber should be aware that these frequencies cannot be used to predict the frequency of adverse events in the course of usual medical practice when patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with frequencies obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis by which to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

**Table 2: Adverse events observed with a frequency of  $\geq$  2% and occurring with a rate greater than placebo**

	Exelon Patch 9.5mg/24h n (%)	Exelon Patch 17.4mg/24h n (%)	Exelon capsule 6 mg BID n (%)	Placebo n (%)
Total patients studied	291	303	294	302
Total no. of patients with AEs	147(51)	200(66)	186(63)	139(46)
Nausea	21(7)	64 (21)	68(23)	15(5)

	Exelon Patch 9.5mg/24h n (%)	Exelon Patch 17.4mg/24h n (%)	Exelon capsule 6 mg BID n (%)	Placebo n (%)
Vomiting	18(6)	57 (19)	50(17)	10(3)
Diarrhea	18(6)	31 (10)	16(5)	10(3)
Depression	11(4)	12 (4)	13(4)	4(1)
Headache	10(3)	13 (4)	18(6)	5(2)
Anxiety	9(3)	8 (3)	5(2)	4(1)
Anorexia/Decreased appetite	9(3)	27 (9)	26(9)	6(2)
Weight decreased	8(3)	23 (8)	16(5)	4(1)
Dizziness	7(2)	21 (7)	22(7)	7(2)
Abdominal pain	7(2)	11 (4)	4(1)	2(1)
Urinary tract infection	6(2)	5 (2)	4(1)	3(1)
Asthenia	5(2)	9 (3)	17(6)	3(1)
Fatigue	5(2)	7 (2)	2(1)	4(1)
Insomnia	4(1)	12 (4)	6(2)	6(2)
Abdominal pain upper	3(1)	8 (3)	6(2)	6(2)
Vertigo	0(0)	7 (2)	4(1)	3(1)

### Incidence of application site reactions

The vast majority of patients participating in the controlled clinical trial had either no observed skin irritation or mild to moderate skin reactions. The incidence of severe reactions was very low regardless of administered dosage.

### 6.2 Other adverse events observed during clinical trials

Exelon Patch has been administered to 1071 patients with Alzheimer's disease during clinical trials worldwide. Of these, 869 patients have been treated for at least 3 months, 706 patients have been treated for at least 6 months, and 212 patients have been treated for 1 year.

Treatment-emergent signs and symptoms that occurred during 1 controlled and 4 open-label trials in North America, Europe, Latin America, Asia and Japan were recorded as adverse events by the clinical investigators using terminology of their own choosing.

To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using the MedDRA dictionary, and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 1071 patients from these trials who experienced that event while receiving the Exelon Patch. All patch doses are pooled.

All adverse events occurring in at least 1 patient (approximately 0.1%) are included, except for those already listed elsewhere in labeling, too general to be informative, or relatively minor events.

Events are classified by system organ class and listed using the following definitions: **Frequent** – those occurring in at least 1/100 patients; **Infrequent** – those occurring in 1/100 to 1/1,000 patients. These adverse events are not necessarily related to Exelon Patch treatment and in most cases were

observed at a similar frequency in placebo-treated patients in the controlled studies.

**Blood and Lymphatic System Disorders: Frequent:** Anemia.

**Cardiac Disorders: Infrequent:** Angina pectoris, cardiac failure, bradycardia, atrial fibrillation, supraventricular extrasystoles, myocardial infarction, tachycardia, arrhythmia, atrioventricular block.

**Ear and Labyrinth Disorders: Infrequent:** Tinnitus.

**Eye Disorders: Infrequent:** Cataract, glaucoma, vision blurred.

**Gastrointestinal System: Frequent:** Constipation, gastritis. **Infrequent:** Gastroesophageal reflux disease, hemochezia, peptic ulcer, hematemesis, pancreatitis, salivary hypersecretion.

**General Disorders and Administration Site Conditions: Infrequent:** Application site dermatitis, application site irritation, peripheral edema, chest pain, application site eczema, hyperpyrexia.

**Hepatobiliary Disorders: Infrequent:** Cholecystitis.

**Infections and Infestations: Frequent:** Nasopharyngitis, pneumonia. **Infrequent:** Diverticulitis.

**Injury, Poisoning and Procedural Complications: Frequent:** Fall. **Infrequent:** Hip fracture, subdural hematoma.

**Investigations: Infrequent:** Blood creatine phosphokinase increased, lipase increased, blood amylase increased, electrocardiogram QT prolonged.

**Metabolic and Nutritional Disorders: Frequent:** Dehydration **Infrequent:** Hyperlipidemia, hypokalemia, hyponatremia.

**Musculoskeletal and Connective Tissue Disorders: Infrequent:** Arthralgia, muscle spasms, myalgia.

**Nervous System Disorders: Frequent:** Tremor. **Infrequent:** Migraine, parkinsonism, epilepsy.

**Psychiatric Disorders: Infrequent:** Delusion.

**Renal and Urinary Disorders: Frequent:** Urinary incontinence. **Infrequent:** Pollakiuria, hematuria, nocturia, renal failure.

**Reproductive System and Breast Disorders: Infrequent:** Benign prostatic hyperplasia.

**Respiratory, Thoracic, and Mediastinal Disorders: Infrequent:** Dyspnea, bronchospasm, chronic obstructive pulmonary disease.

**Skin and Subcutaneous Tissue Disorders: Frequent:** Pruritus. **Infrequent:** Erythema, eczema, dermatitis, rash erythematous, skin ulcer.

**Vascular Disorders: Infrequent:** Hypotension.

## 7 DRUG INTERACTIONS

No specific interaction studies have been conducted with the Exelon Patch (rivastigmine transdermal system).

### 7.1 Effect of Exelon on the Metabolism of Other Drugs

Rivastigmine is primarily metabolized through hydrolysis by esterases. Minimal metabolism occurs via the major cytochrome P450 isoenzymes. Based on *in-vitro* studies, no pharmacokinetic drug interactions with drugs metabolized by the following isoenzyme systems are expected: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, or CYP2C19.

No pharmacokinetic interaction was observed between rivastigmine taken orally 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.

### 7.2 Effect of Other Drugs on the Metabolism of Exelon

Drugs that induce or inhibit CYP450 metabolism are not expected to alter the metabolism of rivastigmine.

Population PK analysis with a database of 625 patients showed that the pharmacokinetics of rivastigmine taken orally were not influenced by commonly prescribed medications such as antacids (n=77), antihypertensives (n=72),  $\beta$ -blockers (n=42), calcium channel blockers (n=75), antidiabetics (n=21), nonsteroidal anti-inflammatory drugs (n=79), estrogens (n=70), salicylate analgesics (n=177), antianginals (n=35) and antihistamines (n=15).

### 7.3 Use with Anticholinergics, cholinomimetics and other cholinesterase inhibitors

In view of its pharmacodynamic effects, rivastigmine should not be given concomitantly with other cholinomimetic drugs and might interfere with the activity of anticholinergic medications. A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

**Pregnancy Category B:** There are no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, the Exelon Patch should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

No dermal reproduction studies in animals have been conducted. Oral reproduction studies conducted in pregnant rats at doses up to 2.3 mg-base/kg/day and in pregnant rabbits at doses up to 2.3 mg-base/kg/day revealed no evidence of teratogenicity. Studies in rats showed slightly decreased fetal/pup weights, usually at doses causing some maternal toxicity.

### 8.3 Nursing Mothers

Milk transfer studies in animals have not been conducted with dermal rivastigmine. In rats given rivastigmine orally, concentrations of rivastigmine plus metabolites were approximately two times higher in milk than in plasma. It is not known whether rivastigmine is excreted in human breast milk. Exelon Patch (rivastigmine transdermal system) has no indication for use in nursing mothers.

### 8.4 Pediatric Use

There are no adequate and well-controlled trials documenting the safety and efficacy of Exelon in any illness occurring in children.

### 8.5 Geriatric Use

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

### 8.6 Hepatic Disease

No pharmacokinetic study was conducted with the Exelon Patch in subjects with hepatic impairment. Following a single 3-mg dose, mean oral clearance of rivastigmine was 60% lower in hepatically impaired patients (n=10, biopsy proven) than in healthy subjects (n=10). After multiple 6-mg BID oral dosing, the mean clearance of rivastigmine was 65% lower in mild (n=7, Child-Pugh score 5-6) and moderate (n=3, Child-Pugh score 7-9) hepatically impaired patients (biopsy proven, liver cirrhosis) than in healthy subjects (n=10). Dosage

adjustment is not necessary in hepatically impaired patients as the dose of drug is individually titrated to tolerability.

### 8.7 Renal Disease

No study was conducted with the Exelon Patch in subjects with renal impairment. Following a single 3-mg dose, mean oral clearance of rivastigmine is 64% lower in moderately impaired renal patients (n=8, GFR=10-50 mL/min) than in healthy subjects (n=10, GFR >=60 mL/min); Cl/F=1.7 L/min (cv=45%) and 4.8 L/min (cv=80%), respectively. In severely impaired renal patients (n=8, GFR<10 mL/min), mean oral clearance of rivastigmine is 43% higher than in healthy subjects (n=10, GFR >=60 mL/min); Cl/F=6.9 L/min and 4.8 L/min, respectively. For unexplained reasons, the severely impaired renal patients had a higher clearance of rivastigmine than moderately impaired patients. However, dosage adjustment may not be necessary in renally impaired patients as the dose of the drug is individually titrated to tolerability.

### 8.8 Low Body Weight

Rivastigmine exposure is higher in subjects with low body weight. 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. This suggests special attention should be given to patients with very low body weight during up-titration (see *Dosage and Administration (2)*).

### 8.9 Gender and Race

No specific pharmacokinetic study was conducted to investigate the effect of gender and race on the disposition of Exelon, but a population pharmacokinetic analysis indicates that gender (n=277 males and 348 females) and race (n=575 White, 34 Black, 4 Asian, and 12 Other) did not affect the clearance of Exelon administered orally. Similar results were seen with analyses of pharmacokinetic data obtained after the administration of the Exelon Patch.

### 8.10 Nicotine Use

Population pharmacokinetic analysis showed that nicotine use increases the oral clearance of rivastigmine by 23% (n=75 Smokers and 549 Nonsmokers). No dose adjustment is necessary as the dose of the drug is individually titrated to tolerability.

## 10 OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug. As in any case of overdose, general supportive measures should be utilized.

As rivastigmine has a plasma half-life of about 3.4 hours after patch administration and a duration of acetylcholinesterase inhibition of about 9 hours, it is recommended that in cases of asymptomatic overdose the patch should be immediately removed and no further patch should be applied for the next 24 hours.

As in any case of overdose, general supportive measures should be utilized. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Atypical responses in blood pressure and heart rate have been reported with other drugs that increase cholinergic activity when co-administered with quaternary anticholinergics such as glycopyrrolate. Due to the short plasma elimination half-life of rivastigmine after patch administration, dialysis

(hemodialysis, peritoneal dialysis, or hemofiltration) would not be clinically indicated in the event of an overdose.

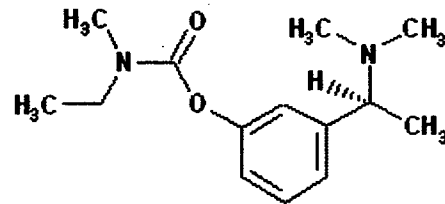
In overdose accompanied by severe nausea and vomiting, the use of antiemetics should be considered. In a documented case of an oral 46-mg overdose with Exelon, the patient experienced vomiting, incontinence, hypertension, psychomotor retardation, and loss of consciousness. The patient fully recovered within 24 hours and conservative management was all that was required for treatment.

There are currently no data on overdose with the Exelon Patch (rivastigmine transdermal system).

## 11 DESCRIPTION

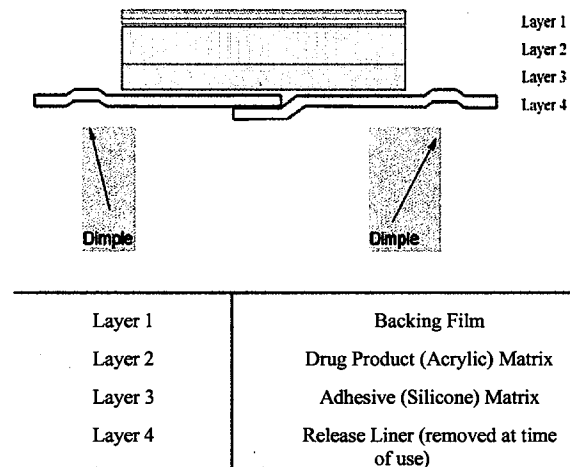
Exelon Patch contains rivastigmine, a reversible cholinesterase inhibitor that is known chemically as (S)- 3-[1-(dimethylamino) ethyl]phenyl ethylmethylcarbamate. It has an empirical formula of C<sub>14</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub> as the base and a molecular weight of 250.34 (as the base). Rivastigmine is a viscous, clear, and colorless to yellow to very slightly brown liquid that is sparingly soluble in water and very soluble in ethanol, acetonitrile, n-octanol and ethyl acetate.

The distribution coefficient at 37°C in n-octanol/phosphate buffer solution pH 7 is 4.27.



Exelon Patch is for transdermal administration. The patch comprises a four-layer laminate containing the backing layer, drug matrix, adhesive matrix and overlapping release liner. The release liner is removed and discarded prior to use. See Figure 1 for a detailed illustration.

Figure 1: Cross Section of the Patch



Excipients within the formulation include acrylic copolymer, poly(butylmethacrylate, methyl-methacrylate), silicone adhesive applied to a flexible polymer backing film, silicone oil, and vitamin E.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Pathological changes in Dementia of the Alzheimer's type and Dementia associated with Parkinson's disease involve cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. These pathways are thought to be intricately involved in memory, attention, learning, and other cognitive processes. While the precise mechanism of rivastigmine's action is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. If this proposed mechanism is correct, rivastigmine's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that rivastigmine alters the course of the underlying dementing process.

### 12.2 Pharmacodynamics

After a 6-mg oral dose of rivastigmine in humans, anticholinesterase activity is present in CSF for about 10 hours, with a maximum inhibition of about 60% 5 hours after dosing.

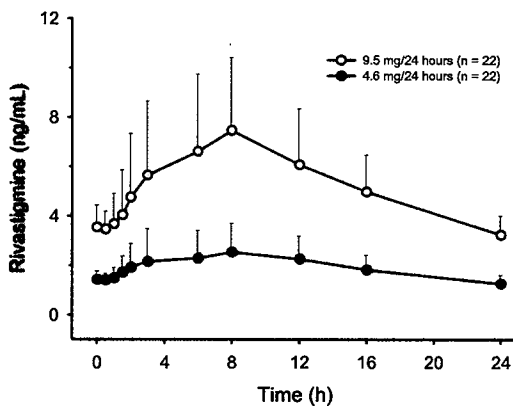
*In-vitro* and *in-vivo* studies demonstrate that the inhibition of cholinesterase by rivastigmine is not affected by the concomitant administration of memantine, an N-methyl-D-aspartate receptor antagonist.

### 12.3 Pharmacokinetics

#### Absorption

After the first dose, there is a lag time of 0.5- 1 hours in the absorption of rivastigmine from the Exelon Patch (rivastigmine transdermal system). Concentrations then rise slowly typically reaching a maximum after 8 hours, although maximum values ( $C_{max}$ ) are often reached at later times as well (10-16 hours). After the peak, plasma concentrations slowly decrease over the remainder of the 24-hour period of application. At steady state, trough levels are approximately 60-80% of peak levels. Fluctuation (between  $C_{max}$  and  $C_{min}$ ) is lower for the Exelon Patch than for the oral formulation. Exelon Patch 9.5 mg/24 hours exhibited exposure approximately the same as that provided by an oral dose of 6 mg twice daily (i.e., 12 mg/day).

Figure 2: Rivastigmine Plasma Concentrations Following Dermal 24-Hour Patch Application



Inter-subject variability in exposure was lower (43-49%) for the Exelon Patch formulation as compared with the oral formulations (73-103%).

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 are approximately doubled, while for a patient with a body weight of 100 kg the concentrations are approximately halved. The effect of bodyweight on drug exposure suggests special attention to patients with very low body weight during up-titration (see *Dosage and Administration (2)*).

Over a 24-hour dermal application, approximately 50% of the drug load is released from the system.

Exposure ( $AUC_{0-24}$ ) to rivastigmine (and metabolite NAP226-90) 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 upon multiple dosing.

#### Distribution

Rivastigmine is weakly bound to plasma proteins (approximately 40%) over the therapeutic range. It readily crosses the blood-brain barrier, reaching CSF peak concentrations in 1.4-2.6 hours. It has an apparent volume of distribution in the range of 1.8-2.7 L/kg.

#### Metabolism

Rivastigmine is extensively metabolized primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite NAP226-90. *In-vitro*, this metabolite shows minimal inhibition of acetylcholinesterase (<10%). Based on evidence from *in-vitro* and animal studies, the major cytochrome P450 isoenzymes are minimally involved in rivastigmine metabolism.

The metabolite-to-parent  $AUC_{0-24}$  ratio was about 0.7 after Exelon Patch application 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. Based on *in vitro* studies, no unique metabolic routes were detected in human skin.

#### Elimination

Renal excretion of the metabolites is the major route of elimination. Unchanged rivastigmine is found in trace amounts in the urine. Following administration of  $^{14}C$ -rivastigmine, renal elimination was rapid and essentially complete (>90%) within 24 hours. Less than 1% of the administered dose is excreted in the feces. The apparent elimination half-life in plasma is approximately 3 hours after patch removal. Renal clearance was approximately 2.1-2.8 L/hr.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In oral carcinogenicity studies conducted at doses up to 1.1 mg-base/kg/day in rats and 1.6 mg-base/kg/day in mice, rivastigmine was not carcinogenic.

In a dermal carcinogenicity study conducted at doses up to 0.75 mg-base/kg/day in mice, rivastigmine was not carcinogenic. The mean rivastigmine plasma exposure



(AUC) at this dose was 0.3-0.4 times that observed in Alzheimer's disease patients at the recommended clinical dose (one Exelon Patch 9.5 mg/24 hours).

Rivastigmine was clastogenic in two in vitro assays in the presence, but not the absence, of metabolic activation. It caused structural chromosomal aberrations in V79 Chinese hamster lung cells and both structural and numerical (polyploidy) chromosomal aberrations in human peripheral blood lymphocytes. Rivastigmine was not genotoxic in three in vitro assays: the Ames test, the unscheduled DNA synthesis (UDS) test in rat hepatocytes (a test for induction of DNA repair synthesis), and the HGPRT test in V79 Chinese hamster cells. Rivastigmine was not clastogenic in the in vivo mouse micronucleus test.

No fertility or reproduction studies have been conducted in animals treated with dermal rivastigmine. Rivastigmine had no effect on fertility or reproductive performance in rats at oral doses up to 1.1 mg-base/kg/day.

#### 14 CLINICAL STUDIES

The effectiveness of the Exelon Patch (rivastigmine transdermal system) in Alzheimer's Disease and dementia associated with Parkinson's Disease was based on the results of a single controlled trial in patients with Alzheimer's Disease (see below) as well as on three controlled trials of the immediate release capsule in Alzheimer's Disease and one controlled trial in dementia associated with Parkinson's Disease (see package insert for the Exelon Capsules and Oral Solution for details).

##### International 24-Week Study of Exelon Patch (rivastigmine transdermal system)

This was a randomized double-blind clinical investigation in patients with Alzheimer's Disease [diagnosed by NINCDS-ADRDA and DSM-IV criteria, Mini-Mental Status Examination (MMSE) score  $\geq 10$  and  $\leq 20$ ]. The mean age of patients participating in this trial was 74 years with a range of 50-90 years. Approximately 67% of patients were women and 33% were men. The racial distribution was Caucasian 75%, Black 1%, Oriental 9% and Other Races 15%.

##### Study Outcome Measures

The effectiveness of the Exelon Patch (rivastigmine transdermal system) was evaluated in this study using a dual outcome assessment strategy.

The ability of the Exelon Patch to improve cognitive performance was assessed with the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog), a multi-item instrument that has been extensively validated in longitudinal cohorts of Alzheimer's disease patients. The ADAS-Cog examines selected aspects of cognitive performance including elements of memory, orientation, attention, reasoning, language and praxis. The ADAS-Cog scoring range is from 0 to 70, with higher scores indicating greater cognitive impairment. Elderly normal adults may score as low as 0 or 1, but it is not unusual for non-demented adults to score slightly higher.

The ability of the Exelon Patch to produce an overall clinical effect was assessed using the Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change (ADCS-CGIC). The ADCS-CGIC is a more standardized form of CIBIC-Plus and is also scored as a seven-point categorical rating, ranging from a score of 1, indicating "markedly improved", to a score of 4, indicating "no change" to a score of 7, indicating "marked worsening".

##### Study Results

In this study, 1195 patients were randomized to one of the following 4 treatments: Exelon Patch 9.5 mg/24 hours,

Exelon Patch 17.4 mg/24 hours, Exelon capsules in a dose of 6 mg BID or placebo. This 24-week study was divided into a 16-week titration phase followed by an 8-week maintenance phase. In the active treatment arms of this study, doses below the target dose were permitted during the maintenance phase in the event of poor tolerability.

##### Effects on the ADAS-Cog

Figure 3 illustrates the time course for the change from baseline in ADAS-Cog scores for all 4 treatment groups over the 24-week study. At 24 weeks, the mean differences in the ADAS-Cog change scores for the Exelon-treated patients, compared to the patients on placebo, were 1.8, 2.9, and 1.8 units for the Exelon Patch 9.5 mg/24 hours, Exelon Patch 17.4 mg/24 hours, and Exelon capsule 6 mg BID groups, respectively. The difference between each of these groups and placebo was statistically significant.

##### Effects on the ADCS-CGIC

Figure 4 is a histogram of the distribution of patients' scores on the ADCS-CGIC for all 4 treatment groups.

At 24 weeks, the mean difference in the ADCS-CGIC scores for the comparison of patients in each of the Exelon-treated groups with the patients on placebo, was 0.2 units. The difference between each of these groups and placebo was statistically significant.

Figure 3: Time Course of the Change from Baseline in ADAS-Cog Score for Patients Observed at Each Time Point

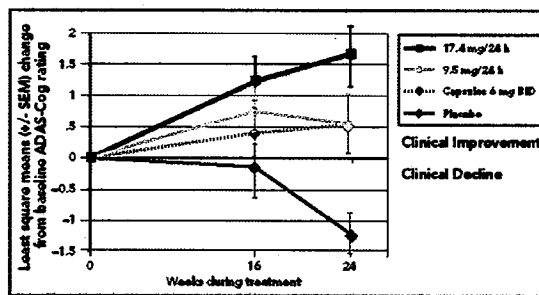
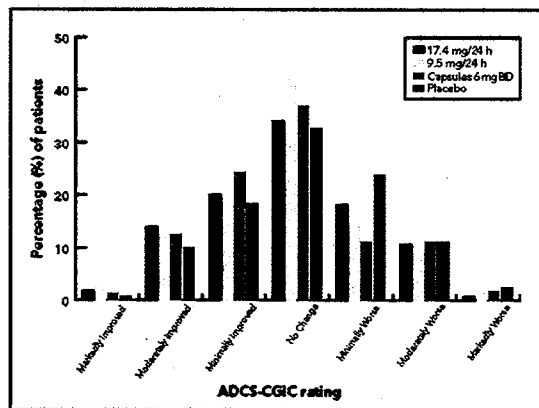


Figure 4: Distribution of ADCS-CGIC Scores for Patients Completing the Study



#### 16 HOW SUPPLIED/STORAGE AND HANDLING

##### Patch 4.6 mg/24 hours

Each patch of 5 cm<sup>2</sup> contains 9 mg rivastigmine base with *in vivo* release rate of 4.6 mg/24 hours.

Carton of 30.....NDC 0078-0501-15

### **Patch 9.5 mg/24 hours**

Each patch of 10 cm<sup>2</sup> contains 18 mg rivastigmine base with *in vivo* release rate of 9.5 mg/24 hours.

Carton of 30.....NDC 0078-0502-15

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Keep Exelon Patch (rivastigmine transdermal system) in the individual sealed pouch until use.

Used systems should be folded, with the adhesive surfaces pressed together, and discarded safely.

Each pouch contains one patch.

## **17 PATIENT COUNSELING INFORMATION**

### **17.1 General**

Patient information is printed in section 17. 8. To assure safe and effective use of the Exelon Patch, this information and instructions provided in the patient information section should be discussed with patients.

### **17.2 Importance of Correct Usage**

Patients or caregivers should be informed of the importance of applying the correct dose on the correct part of their body. They should be instructed to rotate the application site in order to minimize skin irritation. The same site should not be used within 14 days. Patches should be replaced every 24 hours and the time of day should be consistent. It may be helpful for this to be part of a daily routine, such as the daily bath or shower.

Patients or caregivers should be told to avoid exposure of the patch to external heat sources (excess sunlight, saunas, solarium) for long periods of time.

### **17.3 Discarding Used Patches**

Patients or caregivers should be instructed to fold the patch in half after use and to discard it out of the reach and sight of children and pets. They should also be informed that drug still remains in the patch after 24-hour usage. They should be instructed to avoid eye contact and to wash their hands after handling the patch.

### **17.4 Concomitant Use of Drugs with Cholinergic Action**

Patients or caregivers should be told that while wearing Exelon Patch they should not be taking Exelon capsules or Exelon oral solution or other drugs with cholinergic effects.

### **17.5 Gastrointestinal Adverse Events**

Patients or caregivers should be informed of the potential gastrointestinal adverse events such as nausea, vomiting and diarrhea. Patients and caregivers should be instructed to observe for these adverse reactions at all times, and in particular when treatment is initiated or the dose is increased. Patients and caregivers should be instructed to inform their physician if these adverse events persist as a dose adjustment/reduction may be required.

### **17.6 Monitoring the Patient's Weight**

Patients or caregivers should be informed that the Exelon Patch may affect the patient's appetite and/or the patient's weight. Any loss of appetite or weight reduction needs to be monitored.

### **17.7 Missed Doses**

If the patient has missed a dose, he/she should be instructed to apply a new patch immediately. They may apply the next patch at the usual time the next day. Patients should not apply two Exelon patches to make up for one missed.

If treatment has been missed for several days, the patient or caregiver should be informed to restart treatment with the starting patch dose of 4.6 mg/24 hours. Titration to the next patch dose should proceed after 4 weeks (see *Dosage and Administration (2.1)*).

## **17.8 FDA-approved patient labeling**

### **What is the Exelon Patch and what it is used for?**

Exelon belongs to a class of substances called cholinesterase inhibitors. It is used for the treatment of memory disorders in patients with Alzheimer's disease or with Parkinson's disease.

### **Before you apply the Exelon Patch:**

Carefully follow all instructions given to you by your doctor, even if they differ from the information contained in this leaflet.

Read the following information before you apply the Exelon Patch.

### **Do not apply the Exelon Patch in the following cases:**

If you know that you are allergic (hypersensitive) to rivastigmine (the active substance in the Exelon Patch) or to any of the other ingredients of the Exelon Patch (see *Description (11)*).

If you have ever had an allergic reaction to a similar type of medicine.

*If this applies to you, tell your doctor without applying the Exelon Patch.*

### **Take special care with the Exelon Patch if:**

- You have, or ever had an irregular heartbeat.
- You have, or ever had an active stomach ulcer.
- You have, or ever had difficulties in passing urine.
- You have, or ever had seizures.
- You have, or ever had asthma or a severe respiratory disease.
- You suffer from trembling.
- You have a low body weight.
- You have impaired liver function.

If any of these apply to you, your doctor may need to monitor you more closely while you are on this medicine.

If you have not been applying the Exelon Patch for several days do not apply the next patch until you have talked to your doctor.

### **Exelon Patch with food and drink:**

Food or drink does not affect Exelon Patch because rivastigmine enters your bloodstream through your skin.

### **Exelon Patch and older people:**

Exelon Patch can be used by patients over the age of 65.

### **Exelon Patch and children:**

The use of the Exelon Patch in children is not recommended.

### **Pregnant women:**

Tell your doctor if you are pregnant or planning to become pregnant. In the event of pregnancy, the benefits of the Exelon Patch must be assessed against the possible effects on your unborn child. Ask your doctor or pharmacist for advice before taking any medicine during pregnancy.

**Breast-feeding mothers:**

You should not breast-feed during treatment with the Exelon Patch. Ask your doctor or pharmacist for advice before taking any medicine while you are breast-feeding.

**Driving and using machines:**

Your doctor will tell you whether your illness allows you to drive vehicles and use machines safely. Exelon Patch may cause dizziness and drowsiness, mainly at the start of treatment or when increasing the dose. If you feel dizzy or drowsy, do not drive, use machines or perform any other tasks that require your attention.

**Taking other medicines:**

Tell your doctor or pharmacist about any other medicines you are taking or have recently taken, including any you have bought without a prescription.

Exelon Patch should not be given together with other medicines with similar effects (cholinomimetic agents) or with anticholinergic medicines.

If you need to have surgery while using the Exelon Patch, you should inform your doctor because the Exelon Patch may exaggerate the effects of some muscle relaxants during anesthesia.

**How to use the Exelon Patch:**

Follow all instructions given to you by your doctor carefully, even if they differ from the ones given in this leaflet.

This medicine must not be given to children.

Do not eat the Exelon Patch.

You must remove the previous day's Exelon Patch *before* applying a new one. Do not cut the patch into pieces.

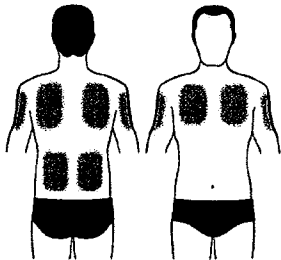
**How to start treatment:**

Your doctor will tell you which Exelon Patch is suitable for you. Treatment usually starts with the Exelon Patch 4.6 mg/24 hours, and after several weeks many patients move to Exelon Patch 9.5 mg/24 hours as the usual daily dose. The patch should be replaced by a new one after 24 hours.

During the course of treatment, your doctor may adjust the dose to suit your individual needs.

If you have not been applying the Exelon Patch for several days do not apply the next patch before you have talked to your doctor.

**Where to apply the Exelon Patch:**



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

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

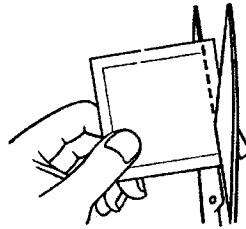
- clean, dry and hairless

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

When changing your patch, apply your new patch to a different spot of skin (for example on the right side of your body one day, then on the left side the next day). Do not apply a new patch to that same spot for at least 14 days. Only one patch should be worn at a time and the patch should be replaced by a new one after 24 hours.

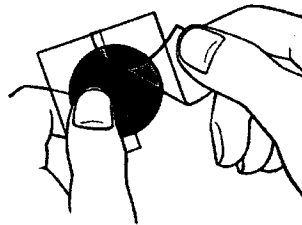
**How to apply the Exelon Patch:**

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

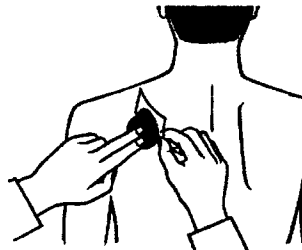


Cut the pouch along the dotted line and remove the patch.

The patch should not be cut or folded sharply.



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



Put the sticky side of the patch on the upper or lower back, upper arm or chest and then peel off the second side of the protective liner.



Then press the patch firmly in place with the hand to make sure that the edges stick well.

You may write (e.g., the day of the week) on the Exelon Patch with a thin ball point pen.

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

#### **How to remove the Exelon Patch:**

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

#### **How to dispose of the Exelon Patch:**

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

#### **Can the Exelon Patch be worn when bathing, swimming, or in the sun?**

Bathing, swimming, or showering should not affect the patch. When swimming, you can wear the patch under your swimsuit. Make sure the patch does not loosen during these activities.

The patch should not be exposed to any external heat sources (excessive sunlight, saunas, solarium) for long periods of time.

#### **What to do if the Exelon Patch falls off:**

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

#### **When and how long to apply the Exelon Patch:**

To benefit from your medicine you must apply a new patch every day.

Tell your caregiver that you are applying Exelon Patch. Also tell your caregiver if you have not been applying Exelon Patch for several days.

#### **What to do if you apply more Exelon Patches than you should:**

If you accidentally apply more Exelon Patches than you should, remove all the Exelon patches from your skin, and then inform your doctor that you have accidentally applied more Exelon Patches than you should have. You may require medical attention. Some people who have accidentally taken too much Exelon have experienced nausea, vomiting, diarrhea, high blood pressure and hallucinations. Slow heartbeat and fainting may also occur.

#### **If you forget to apply the Exelon Patch:**

If you find you have forgotten to apply your Exelon Patch, apply a new patch immediately. You may apply the next patch at the usual time the next day. Do not apply two Exelon patches to make up for the one that you missed.

If you have not been applying the Exelon Patch for several days do not apply the next patch before you have talked to your doctor.

#### **Possible side effects:**

Like all medicines, the Exelon Patch can cause side effects, although not everybody gets them.

Do not be alarmed by this list of possible side effects. You may not experience any of them.

You may tend to see side effects more frequently when you start your medication or increase to a higher dose. In most cases, side effects will gradually disappear as your body becomes used to the medicine. Gastrointestinal reactions such as nausea (feeling sick) and vomiting (being sick) are the most common side effects. The other common side effects are: loss of appetite, anxiety, difficulty in sleeping, dizziness, headache, diarrhea, stomach discomfort after meals, stomach pain, skin reactions at the application site (redness, itching, irritation, swelling), fatigue, weakness, and weight loss.

#### **Some side effects could become serious:**

**Common:** depression.

**Uncommon:** severe confusion, hallucinations, vascular accident involving the brain (loss of coordination, difficulty in speaking or breathing and signs of brain disorder), fainting, problems with heart rhythm (irregular or fast or slow heart beat), gastric ulcer and gastrointestinal hemorrhage (blood in stools or when vomiting).

If you experience any of these, remove the Exelon Patch *and tell your doctor right away.*

#### **Other side effects:**

**Uncommon:** agitation, drowsiness, sweating and a general feeling of being unwell.

If any of these affects you severely, *tell your doctor.*

Additional side effects have been reported with Exelon capsules or oral solution:

**Common:** confusion and trembling.

**Uncommon:** changes in liver function tests and accidental falls.

**Rare:** convulsions, chest pain, duodenal ulcer and rashes.

**Very rare:** urinary tract infection, high blood pressure, inflammation of the pancreas (severe upper stomach pain, often with nausea and vomiting) and severe vomiting that can lead to a rupture of the esophagus.

In addition, you should contact your doctor or pharmacist if you experience any other possible side effects not mentioned in this leaflet.

#### **How to store the Exelon Patch:**

Do not use the Exelon Patch after the expiration date shown on the carton and pouch.

Store at room temperature, 59-86°F (15-30°C).

Do not use any Exelon Patch that is damaged or shows signs of tampering.

Keep the Exelon Patch out of the reach and sight of children and pets.

**MANUFACTURED BY:**

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Andernach, Germany

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East Hanover, NJ 07936

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