ALOXI (palonosetron HCl) Capsules Initial U.S. Approval: 2003

--- RECENT MAJOR CHANGES ---
Warnings and Precautions, Serotonin Syndrome (5.2) 09/2014

--- INDICATIONS AND USAGE ---
ALOXI Capsules, a serotonin subtype 3 (5-HT3) receptor antagonist, are indicated for:
• Moderately emetogenic cancer chemotherapy -- prevention of acute nausea and vomiting associated with initial and repeat courses (1.1)

--- DOSAGE AND ADMINISTRATION ---
Adult Dosage: one 0.5 mg capsule administered approximately one hour prior to the start of chemotherapy (2.1)
ALOXI can be taken with or without food (12.3)

--- DOSAGE FORMS AND STRENGTHS ---
0.5 mg capsule (3)

--- CONTRAINDICATIONS ---
ALOXI is contraindicated in patients known to have hypersensitivity to the drug or any of its components (4)

--- WARNINGS AND PRECAUTIONS ---
• Hypersensitivity reactions may occur in patients who have exhibited hypersensitivity to other 5-HT3 receptor antagonists (5.1)
• Serotonin syndrome has been reported with 5-HT3 receptor antagonists alone but particularly with concomitant use of serotonergic drugs (5.2)

--- ADVERSE REACTIONS ---
No adverse reactions have been reported at an incidence of ≥5% for the 0.5 mg dose. Headache and constipation are the most common adverse reactions but occur less frequently (6)

To report SUSPECTED ADVERSE REACTIONS, contact EISAI at 1-888-422-4743 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

--- DRUG INTERACTIONS ---
The potential for clinically significant drug interactions with palonosetron appears to be low (7)

--- USE IN SPECIFIC POPULATIONS ---
Safety and effectiveness in patients below the age of 18 years have not been established (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 09/2014
1  INDICATIONS AND USAGE
1.1 Prevention of Chemotherapy-Induced Nausea and Vomiting
ALOXI Capsules are indicated for:

- Moderately emetogenic cancer chemotherapy - prevention of acute nausea and vomiting associated with initial and repeat courses

2  DOSAGE AND ADMINISTRATION
2.1 Recommended Dosing
Dosage for Adults - one 0.5 mg capsule administered approximately one hour prior to the start of chemotherapy. ALOXI can be taken with or without food.

3  DOSAGE FORMS AND STRENGTHS
Capsules, 0.5 mg

4  CONTRAINDICATIONS
ALOXI is contraindicated in patients known to have hypersensitivity to the drug or any of its components.

5  WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity
Hypersensitivity reactions may occur in patients who have exhibited hypersensitivity to other 5-HT3 receptor antagonists. Hypersensitivity reactions have been very rarely reported postmarketing for intravenous palonosetron: dyspnea, bronchospasm, swelling/edema, erythema, pruritus, rash, urticaria. No hypersensitivity reactions have been reported for oral palonosetron.

5.2 Serotonin Syndrome
The development of serotonin syndrome has been reported with 5-HT3 receptor antagonists. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of another 5-HT3 receptor antagonist alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT3 receptor antagonist use occurred in a post-anesthesia care unit or an infusion center.

Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of Aloxi and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue Aloxi and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if Aloxi is used concomitantly with other serotonergic drugs [see Drug Interactions (7), Patient Counseling Information (17)].

6  ADVERSE REACTIONS
6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials for the prevention of nausea and vomiting induced by moderately emetogenic chemotherapy, 693 adult patients received oral palonosetron in doses ranging from 0.25 mg to 0.75 mg. Following is a listing of drug-related adverse reactions reported by >2% of patients from two clinical trials.

Table 1: Adverse Reactions ≥2% from Chemotherapy-Induced Nausea and Vomiting Studies

<table>
<thead>
<tr>
<th>Event</th>
<th>0.25 mg (N=157)</th>
<th>0.5 mg (N=161)</th>
<th>0.75 mg (N=375)</th>
<th>0.25 mg I.V. (N=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>6 (3.8%)</td>
<td>6 (3.7%)</td>
<td>21 (5.6%)</td>
<td>14 (8.6%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (0.6%)</td>
<td>1 (0.6%)</td>
<td>9 (2.4%)</td>
<td>5 (3.1%)</td>
</tr>
</tbody>
</table>

The infrequently reported adverse reactions listed below, assessed by investigators as treatment-related or causality unknown/missing, occurred following administration of ALOXI Capsules to adult patients receiving concomitant cancer chemotherapy. Of these adverse events, fatigue (incidence 1%), was the only adverse event reported at an incidence of ≥1%. In general, adverse reactions were similar between oral and I.V. formulations.

Blood and Lymphatic System: <1%: anemia.
Cardiovascular: <1%: hypertension, transient arrhythmia, first degree atrioventricular block, second degree atrioventricular block, QTc prolongation.
Hearing and Labyrinth: <1%: motion sickness.
Eye: <1%: eye swelling.
Gastrointestinal System: <1%: gastritis, nausea, vomiting.
General: 1%: fatigue, <1%: chills, pyrexia.
Infections: <1%: sinusitis.
Liver: <1%: transient, asymptomatic increases in bilirubin.
Nutrition: <1%: anorexia.
Musculoskeletal: <1%: joint stiffness, myalgia, pain in extremity.
Nervous System: <1%: postural dizziness, dysgeusia.
Psychiatric: <1%: insomnia.
Respiratory System: <1%: dyspnea, epistaxis.
Skin: <1%: generalized pruritus, erythema, alopecia.

Very rare cases (<1/10,000) of hypersensitivity reactions have been reported for I.V. ALOXI from post-marketing experience.

7  DRUG INTERACTIONS
Palonosetron is eliminated from the body through both renal excretion and metabolic pathways with the latter mediated via multiple CYP enzymes. Further in vitro studies indicated that palonosetron is not an inhibitor of CYP1A2, 2C6, 2C8, 2C9, 2D6, 2E1 and 3A4/5 (CYP2C19 was not investigated) nor does it induce the activity of CYP1A2, 2C8, 2D6, or 3A4/5. Therefore, the potential for clinically significant drug interactions with palonosetron appears to be low.

Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT3 receptor antagonists and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) [see Warnings and Precautions (5.2)].

A study in healthy volunteers involving single-dose I.V. palonosetron (0.75 mg) and steady state oral metoclopramide (10 mg four times daily) demonstrated no significant pharmacokinetic interaction.

Concomitant administration of an antacid (Maalox® liquid 30 mL) had no effect on the oral absorption or pharmacokinetics of a single capsule of palonosetron 0.75 mg in healthy subjects.

In controlled clinical trials, ALOXI Capsules have been safely administered with chemotherapeutic agents, systemic corticosteroids, analgesics, and drugs for gastrointestinal disorders including function gastrointestinal disorders, acid-related disorders, and antiemetics/antiemetics.

Palonosetron did not inhibit the antitumor activity of the five chemotherapeutic agents tested (cisplatin, cyclophosphamide, cytarabine, doxorubicin and mitomycin C) in murine tumor models.
This dose group had a similar incidence of adverse events compared to the other dose groups and no dose response effects were observed.

Dialysis studies have not been performed, however, due to the large volume of distribution, dialysis is unlikely to be an effective treatment for palonosetron overdose. A single oral dose of palonosetron at 500 mg/kg in rats and 100 mg/kg in dogs (7673 and 5115 times the recommended human oral dose, respectively, based on body surface area) was lethal. The major signs of toxicity included convulsions, labored breathing, and salivation.

11 DESCRIPTION

ALOXI (palonosetron HCl) Capsules is an antineptic and antinauseant agent. It is a serotonin subtype 3 (5-HT3) receptor antagonist with a strong binding affinity for this receptor. Chemically, palonosetron hydrochloride is: (3αS)-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1H-benzo[d]isoquinoline hydrochloride. The empirical formula is C19H24N2O.HCl, with a molecular weight of 332.87. Palonosetron hydrochloride exists as a single isomer and has the following structural formula:

![Structural formula of palonosetron hydrochloride](image)

Palonosetron hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, soluble in propylene glycol, and slightly soluble in ethanol and 2-propanol.

Each light beige opaque soft gelatin ALOXI Capsule contains 0.56 mg of palonosetron HCl equivalent to palonosetron 0.5 mg. Inactive ingredients are: mono- and di-glycerides of capryl-capric acid, glycerin, polyglyceryl oleate, water, and butylated hydroxyanisole.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Palonosetron is a 5-HT3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors.

Cancer chemotherapy may be associated with a high incidence of nausea and vomiting, particularly when certain agents, such as cisplatin, are used. 5-HT3 receptors are located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone of the area postrema. It is thought that chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine and that the released serotonin then activates 5-HT3 receptors located on vagal afferents to initiate the vomiting reflex.

12.2 Pharmacodynamics

In non-clinical studies palonosetron possesses the ability to block ion channels involved in ventricular de- and re-polarization and to prolong action potential duration.

The effect of palonosetron on QTc interval was evaluated in a double blind, randomized, parallel, placebo and positive (moxifloxacin) controlled trial in adult men and women. The objective was to evaluate the ECG effects of intravenously administered palonosetron at single doses of 0.25 mg, 0.75 mg or 2.25 mg in 221 healthy subjects. The study demonstrated no significant effect on any ECG interval including QTc duration (cardiac repolarization) at doses up to 2.25 mg.

Clinical trials revealed that oral palonosetron had comparable effects on blood pressure, heart rate, and ECG parameters as intravenous palonosetron.

12.3 Pharmacokinetics

Absorption

Following oral administration, palonosetron is well absorbed with its absolute bioavailability reaching 97%. After single oral doses using buffered solution mean maximum palonosetron concentrations (Cmax) and area under the concentration-time curve (AUC0-∞) were dose proportional over the dose range of 3.0 to 80 µg/kg in healthy subjects.

In 36 healthy male and female subjects given a single oral dose of ALOXI Capsules 0.5 mg, maximum plasma palonosetron concentration (Cmax) was 0.81±1.66 ng/mL (mean ± SD) and time to maximum concentration (Tmax) was 5.1± 1.7 hours. In female subjects (n=18), the mean AUC was 35% higher and the mean Cmax was 26% higher in male subjects (n=18).
In 12 cancer patients given a single oral dose of palonosetron 0.5 mg one hour prior to chemotherapy, Cmax was 0.93±0.34 ng/mL and Tmax was 5.1±5.9 hours. The AUC was 30% higher in cancer patients than in healthy subjects. The mean PK parameters after a single oral dose of 0.5 mg palonosetron are compared between healthy subjects and cancer patients (Table 2).

Table 2: Mean PK parameters1 (± SD) of palonosetron after a single dose of 0.5 mg ALOXI Capsules in healthy subjects and cancer patients

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>Healthy subjects (n=36)</th>
<th>Cancer patients (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>0.81 ± 0.17</td>
<td>0.93 ± 0.34</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>5.1 ± 1.7</td>
<td>5.1 ± 5.9</td>
</tr>
<tr>
<td>AUC (ng·h/mL)</td>
<td>38.2 ± 11.7</td>
<td>49.7±12.2</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>37 ± 12</td>
<td>48 ± 19</td>
</tr>
</tbody>
</table>

1 a study-drug comparison

A high fat meal did not affect the Cmax and AUC of oral palonosetron. Therefore, ALOXI Capsules may be taken without regard to meals.

Distribution
Palonosetron has a volume of distribution of approximately 8.3 ± 2.5 L/kg. Approximately 62% of palonosetron is bound to plasma proteins.

Metabolism
Palonosetron is eliminated by multiple routes with approximately 50% metabolized to form two primary metabolites: N-oxide-palonosetron and 6-hydroxy-palonosetron. These metabolites each have less than 1% of the 5-HT3 receptor antagonist activity of palonosetron. In vitro metabolism studies have suggested that CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in the metabolism of palonosetron. However, clinical pharmacokinetic parameters are not significantly different between poor and extensive metabolizers of CYP2D6 substrates.

Elimination
Following administration of a single oral 0.75 mg dose of [14C]-palonosetron to six healthy subjects, 85% to 93% of the total radioactivity was excreted in urine, and 5% to 8% was eliminated in feces. The amount of unchanged palonosetron excreted in the urine represented approximately 40% of the administered dose. In healthy subjects given ALOXI Capsules 0.5 mg, the terminal elimination half-life (t½) of palonosetron was 37 ± 12 hours (mean ± SD), and in cancer patients, t½ was 48 ± 19 hours. After a single-dose of approximately 0.75 mg intravenous palonosetron, the total body clearance of palonosetron in healthy subjects was 160 ± 35 mL/h/kg (mean ± SD) and renal clearance was 66.5 ± 18.2 mL/h/kg.

Special Populations
[see USE IN SPECIFIC POPULATIONS (8.5-8.9)]

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week carcinogenicity study in CD-1 mice, animals were treated with oral doses of palonosetron at 10, 30 and 60 mg/kg/day. Treatment with palonosetron was not tumorigenic. The highest tested dose produced a systemic exposure to palonosetron (Plasma AUC) of about 90 to 173 times the human exposure (AUC= 49.7 ng·h/mL) at the recommended oral dose of 0.5 mg. In a 104-week carcinogenicity study in Sprague-Dawley rats, male and female rats were treated with oral doses of 15, 30 and 60 mg/kg/day and 15, 45 and 90 mg/kg/day, respectively. The highest doses produced a systemic exposure to palonosetron (Plasma AUC) of 82 and 185 times the human exposure at the recommended dose. Treatment with palonosetron produced increased incidences of adrenal benign pheochromocytoma and combined benign and malignant pheochromocytoma, increased incidences of pancreatic islet cell adenoma and combined adenoma and carcinoma and pituitary adenoma in male rats. In female rats, it produced hepatocellular adenoma and carcinoma and increased the incidences of thyroid C-cell adenoma and combined adenoma and carcinoma.

Palonosetron was not genotoxic in the Ames test, the Chinese hamster ovarian cell (CHO/HGPRT) forward mutation test, the ex vivo hepatocyte unscheduled DNA synthesis (UDS) test or the mouse micronuclet test. It was, however, positive for clastogenic effects in the Chinese hamster ovarian (CHO) cell chromosomal aberration test.

Palonosetron at oral doses up to 60 mg/kg/day (about 921 times the recommended human oral dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

14 CLINICAL STUDIES

Study 1 was a multicenter, randomized, double-blind active control clinical trial of 635 patients set to receive moderately emetogenic cancer chemotherapy. A single-dose of 0.25 mg, 0.5 mg, or 0.75 mg oral ALOXI capsules given one hour prior to moderately emetogenic chemotherapy was compared to a single-dose of 0.25 mg I.V. ALOXI given 30 minutes prior to chemotherapy. Patients were randomized to either dexamethasone or placebo in addition to their assigned treatment. The majority of patients in the study were women (73%), white (69%), and naïve to previous chemotherapy (59%). The primary efficacy endpoint was Complete Response (no emetic episodes and no rescue medication) assessed in the acute phase (0-24 hours). A key secondary efficacy endpoint was Complete Response assessed in the delayed phase (24-120 hours). Other secondary endpoints included Complete Response for the acute plus delayed phases (0-120 hours) and No Nausea for the acute and delayed phases.

Efficacy was based on demonstrating non-inferiority of oral palonosetron doses compared to the approved I.V. formulation. Non-inferiority criteria were met if the lower bound of the two-sided 98.3% confidence interval for the difference in complete response rates of oral palonosetron dose minus approved I.V. formulation was larger than -15%. The non-inferiority margin was 15%.

Efficacy Results
As shown in Table 3, ALOXI Capsules 0.5 mg demonstrated non-inferiority to the active comparator during the 0 to 24 hour time interval; however, for the 24 to 120 hour time period, non-inferiority was not shown. The additional two oral palonosetron dose levels showed similar results.

Table 3: Proportion of Patients Achieving Complete Response Post-Chemotherapy

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Oral ALOXI 0.5 mg (N=160)</th>
<th>I.V. ALOXI 0.25 mg (N=162)</th>
<th>Difference [Two-sided 98.3% Confidence Interval]*: Oral ALOXI minus I.V. ALOXI Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-24 hr</td>
<td>76.3%</td>
<td>70.4%</td>
<td>-5.9% [6.5%, 18.2%]</td>
</tr>
<tr>
<td>24-120 hr</td>
<td>62.5%</td>
<td>65.4%</td>
<td>-2.9% [-16.3%, 10.5%]</td>
</tr>
</tbody>
</table>

* To adjust for multiplicity of treatment groups, a lower-bound of a two-sided 98.3% confidence interval was used to compare to -15%, the negative value of the non-inferiority margin.

As indicated in the data above, analysis of the key secondary endpoint showed that a single dose of ALOXI Capsules 0.5 mg was numerically similar to a single dose of I.V. ALOXI 0.25 mg, however, statistical non-inferiority was not demonstrated. For ALOXI Capsules 0.5 mg versus I.V. ALOXI 0.25 mg, the proportion of patients with complete response at 0-120 hours was 58.8% versus 59.3%, respectively. The proportions of patients with no nausea at 0-24 and 24-120 hours were also numerically similar between oral and I.V. doses.

Study 2 was a multicenter, open label, repeat cycle study performed to evaluate the safety and efficacy of single dose oral ALOXI Capsules 0.75 mg in cancer patients receiving moderately emetogenic chemotherapy. An ALOXI capsule was given to 217 cancer patients in 654 chemotherapy cycles one hour before the start of chemotherapy. Approximately 74% of patients also received single dose oral or intravenous dexamethasone 30 minutes before chemotherapy. Complete Response was not formally evaluated for the repeat cycle application. However, in general the antiemetic effect for the 0-24 hour interval was similar throughout the consecutively repeated cycles.

16 HOW SUPPLIED/STORAGE AND HANDLING

NDC #62856-799-05, ALOXI Capsules, 0.5 mg (free base), are supplied as light beige opaque soft gelatin capsules, five capsules per bottle, each bottle packaged in a small carton.

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

Reference ID: 3629724
Instructions for Patients

Advise patients of the possibility of serotonin syndrome, especially with concomitant use of Aloxi and another serotonergic agent such as medications to treat depression and migraines. Advise patients to seek immediate medical attention if the following symptoms occur: changes in mental status, autonomic instability, neuromuscular symptoms with or without gastrointestinal symptoms [see Warnings and Precautions (5.2)].

Patients should be instructed to read the Patient Information.
Patient Information

ALOXI® (Ah-lock-see)
(palonosetron HCl)
Capsules

Read the Patient Information that comes with ALOXI before you start taking it and each time you refill your prescription. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is ALOXI?
ALOXI is a prescription medicine used in adults to help prevent the nausea and vomiting that happens with certain anti-cancer medicines (chemotherapy).

It is not known if ALOXI is safe and effective in people under the age of 18 years.

Who should not take ALOXI?
Do not take ALOXI if you are allergic to any of the ingredients in ALOXI. See the end of this leaflet for a complete list of ingredients in ALOXI.

What should I tell my doctor before taking ALOXI?
Tell your doctor about all of your medical conditions, including if you:

- have had an allergic reaction to another medicine for nausea or vomiting, such as Kytril (granisetron), Anzemet (dolasetron), Zofran (ondansetron), or to the medicine Lotronex (alosetron).
- are pregnant. It is not known if ALOXI may harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breast-feeding or plan to breast-feed. It is not known if ALOXI passes into your milk. You and your doctor should decide if you will take ALOXI or breast-feed. You should not do both.

How should I take ALOXI?
- Take ALOXI exactly as prescribed by your doctor.
- Take one ALOXI Capsule by mouth about one hour before you get your anti-cancer medicine (chemotherapy).
- ALOXI can be taken with or without food.
- If you take too much ALOXI, tell your doctor right away.

What are the possible side effects of ALOXI?

Serious allergic reactions. Serious allergic reactions can happen with ALOXI. Tell your doctor if you experience redness or swelling of the skin, itching, chest discomfort or shortness of breath.

The most common side effects of ALOXI are:
- headache
- constipation
- tiredness (fatigue)
Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of ALOXI. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store ALOXI?**
- Store ALOXI at 59°F to 86°F (15°C to 30°C).
- Keep ALOXI away from light

**Keep ALOXI out of the reach of children.**

**General information about ALOXI**
Medicines are sometimes prescribed for conditions other than those listed in patient information leaflets. Do not take ALOXI for a condition for which it was not prescribed. Do not give ALOXI to other people even if they have the same condition that you have. It may harm them.

This leaflet summarizes the most important information about ALOXI. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about ALOXI that is written for health professionals. For more information call 1-888-422-4743, or go to www.ALOXI.com.

**What are the ingredients in ALOXI?**
Active ingredient: palonosetron hydrochloride
Inactive ingredients: Mono-glycerides and di-glycerides of capryl/capric acid, glycerin, polyglyceryl oleate, water, and butylated hydroxyanisole

Jointly manufactured by Catalent Pharma Solutions, Somerset NJ and Philadelphia PA, USA, and Helsinn Birex Pharmaceuticals, Dublin, Ireland
HELISNN, Manufactured for Helsinn Healthcare SA, Switzerland

Distributed and marketed by Eisai Inc., Woodcliff Lake, NJ 07677

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