NEW DRUG APPROVAL

Brand Name	Adlarity®
Generic Name	donepezil hydrochloride
Drug Manufacturer	Corium, Inc.

New Drug Approval

FDA approval date: March 11, 2022

Review designation: Standard

Type of review: Type 3 - New Dosage Form; New Drug Application (NDA): 212304

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Dementia is a general term that refers to a decline in cognitive ability severe enough to interfere with activities of daily living. Alzheimer's disease (AD) is the most common type of dementia, accounting for at least two-thirds of cases of dementia in people aged 65 and older. Alzheimer's disease is a neurodegenerative disease with insidious onset and progressive impairment of behavioural and cognitive functions including memory, comprehension, language, attention, reasoning, and judgment. It is the sixth leading cause of death in the United States. Onset before 65 years of age (early onset) is unusual and seen in less than 10% of Alzheimer's disease patients. There is no cure for Alzheimer's disease, although there are treatments available that may improve some symptoms. Alzheimer's disease is classified into preclinical or pre symptomatic, mild, and dementia-stage depending on the degree of cognitive impairment. These stages are different from the DSM-5 classification of Alzheimer's disease. The initial and most common presenting symptom is episodic short-term memory loss with relative sparing of long-term memory and can be elicited in most patients even when not the presenting symptom. Short-term memory impairment is followed by impairment in problem-solving, judgment, executive functioning, lack of motivation and disorganization, leading to problems with multitasking and abstract thinking. In the early stages, impairment in executive functioning ranges from subtle to significant. This is followed by language disorder and impairment of visuospatial skills. Neuropsychiatric symptoms like apathy, social withdrawal, disinhibition, agitation, psychosis, and wandering are also common in the mid to late stages. Difficulty performing learned motor tasks (dyspraxia), olfactory dysfunction, sleep disturbances, extrapyramidal motor signs like dystonia, akathisia, and parkinsonian symptoms occur late in the disease. This is followed by primitive reflexes, incontinence, and total dependence on caregivers.

Alzheimer's disease is typically a disease of old age. The global prevalence of dementia is reported to be as high as 24 million and is predicted to increase 4 times by the year 2050. The estimated health care cost of Alzheimer's disease is $172 billion per year in the United States alone. In 2011, the United States had an estimated 4.5 million people aged sixty-five and above, living with clinical Alzheimer's disease. The incidence of Alzheimer's disease doubles every 5 years, after the age of 65. Age-specific incidence increases significantly from less than 1% per year before 65 years of age to 6% per year after 85 years of age. Prevalence rates increase from 10% after the age of 65 to 40 % after the age of 85. Incidence rates of Alzheimer's disease are slightly higher for women, especially after 85 years of age.

Efficacy

The efficacy of Adlarity® is based on a relative bioavailability study in healthy subjects comparing Adlarity® transdermal system to Aricept® tablets. The clinical studies described below were conducted using donepezil tablets.

Mild to Moderate Alzheimer's Disease-

The effectiveness of donepezil as a treatment for mild to moderate Alzheimer's disease is demonstrated by the results of two randomized, double-blind, placebo-controlled clinical investigations of donepezil tablets in patients with Alzheimer's disease (diagnosed by NINCDS and DSM III-R criteria, Mini-Mental State Examination ≥ 10 and ≤ 26 and Clinical Dementia Rating of 1 or 2). The mean age of patients participating in these donepezil trials was 73 years with a range of 50 to 94. Approximately 62% of patients were women and 38% were men. The racial distribution was white 95%, black 3%, and other races 2%. The higher dose of 10 mg did not provide a statistically significantly greater clinical benefit than 5 mg. There is a suggestion, however, based upon order of group mean scores and dose trend analyses of data from these clinical trials, that a daily dose of 10 mg of donepezil might provide additional benefit for some patients. Accordingly, whether or not to employ a dose of 10 mg is a matter of prescriber and patient preference.

Study Outcome Measures- In each study, the effectiveness of treatment with donepezil was evaluated using a dual outcome assessment strategy. The ability of donepezil 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 patients recruited as participants in each study had mean scores on the ADAS-cog of approximately 26 points, with a range from 4 to 61. Experience based on longitudinal studies of ambulatory patients with mild to moderate Alzheimer's disease suggest that scores on the ADAS-cog increase (worsen) by 6-12 points per year. However, smaller changes may be seen in patients with very mild or very advanced disease since the ADAS-cog is not uniformly sensitive to change over the course of the disease. The annualized rate of decline in the placebo patients participating in donepezil trials was approximately 2 to 4 points per year.

The ability of donepezil to produce an overall clinical effect was assessed using a Clinician's Interview-Based Impression of Change that required the use of caregiver information, the CIBIC-plus. The CIBIC-plus is not a single instrument and is not a standardized instrument like the ADAS-cog. Clinical trials for investigational drugs have used a variety of CIBIC formats, each different in terms of depth and structure.

As such, results from a CIBIC-plus reflect clinical experience from the trial or trials in which it was used and cannot be compared directly with the results of CIBIC-plus evaluations from other clinical trials. The CIBIC- plus used in donepezil trials was a semi-structured instrument that was intended to examine four major areas of patient function: General, Cognitive, Behavioral, and Activities of Daily Living. It represents the assessment of a skilled clinician based upon his/her observations at an interview with the patient, in combination with information supplied by a caregiver familiar with the behavior of the patient over the interval rated. The CIBIC- plus is 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 "markedly worse." The CIBIC-plus has not been systematically compared directly to assessments not using information from caregivers (CIBIC) or other global methods.

Thirty-Week Study- In a study of 30 weeks duration, 473 patients were randomized to receive single daily doses of placebo, 5 mg/day or 10 mg/day of donepezil tablets. The 30-week study was divided into a 24-week double-blind

active treatment phase followed by a 6-week single-blind placebo washout period. The study was designed to compare 5 mg/day or 10 mg/day fixed doses of donepezil tablets to placebo. However, to reduce the likelihood of cholinergic effects, the 10 mg/day treatment was started following an initial 7-day treatment with 5 mg/day doses.

Effects on the ADAS-cog- Figure 1 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 30 weeks of the study. After 24 weeks of treatment, the mean differences in the ADAS-cog change scores for donepezil treated patients compared to the patients on placebo were 2.8 and 3.1 points for the 5 mg/day and 10 mg/day treatments, respectively. These differences were statistically significant. While the treatment effect size may appear to be slightly greater for the 10 mg/day treatment, there was no statistically significant difference between the two active treatments.

Following 6 weeks of placebo washout, scores on the ADAS-cog for both the donepezil treatment groups were indistinguishable from those patients who had received only placebo for 30 weeks. This suggests that the beneficial effects of donepezil abate over 6 weeks following discontinuation of treatment and do not represent a change in the underlying disease. There was no evidence of a rebound effect 6 weeks after abrupt discontinuation of therapy.

Figure 1. Time-course of the changes from Baseline in ADAS-cog Score for Patients Completing 24 Weeks of Treatment

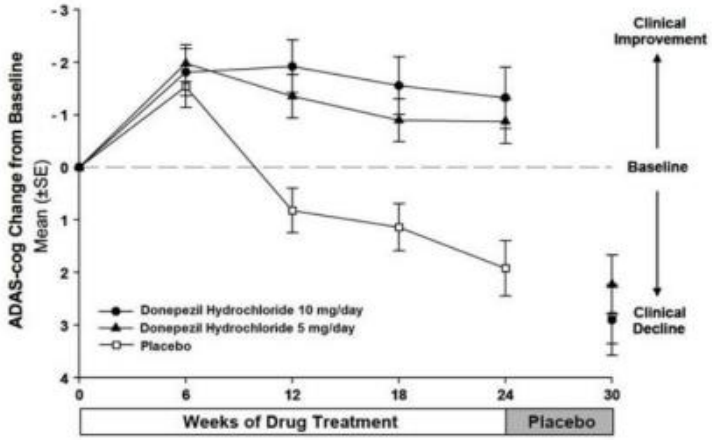
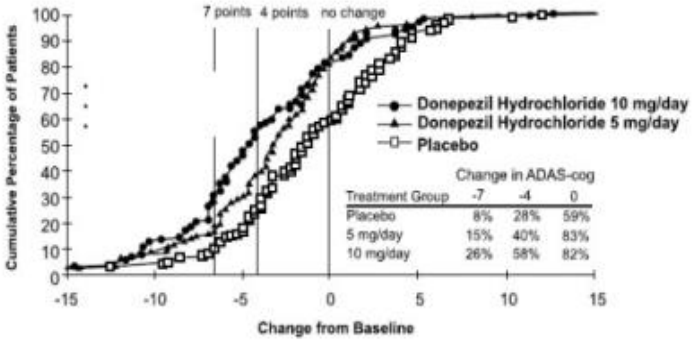


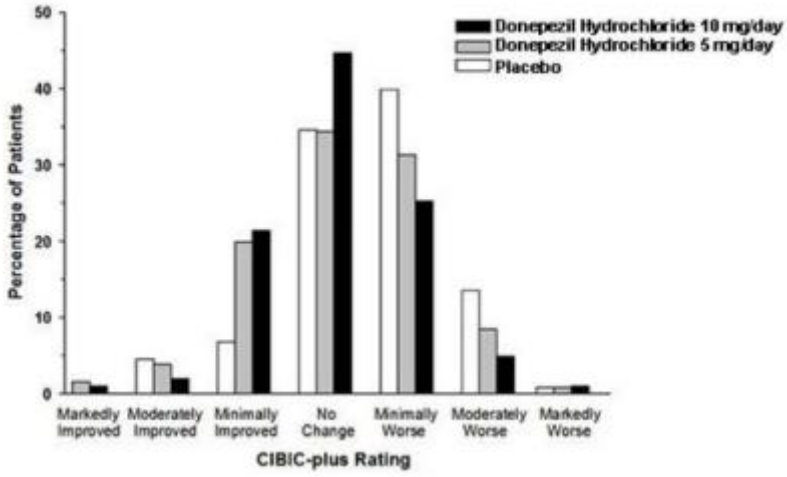
Figure 2 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained the measure of improvement in ADAS-cog score shown on the X-axis. Three change scores (7-point and 4-point reductions from baseline or no change in score) have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table. The curves demonstrate that both patients assigned to placebo and donepezil have a wide range of responses, but that the active treatment groups are more likely to show greater improvements. A curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon or shifted to the right of the curve for placebo.

Figure 2. Cumulative Percentage of Patients Completing 24 Weeks of Doubled- blind Treatment with Specified Changes from Baseline ADAS-cog Scores. The Percentages of Randomized Patients who Completed the Study were: Placebo 80%, 5mg/day 85% and 10 mg/day 68%



Effects on the CIBIC-plus- Figure 3 is a histogram of the frequency distribution of CIBIC-plus scores attained by patients assigned to each of the three treatment groups who completed 24 weeks of treatment. The mean drug-placebo differences for these groups of patients were 0.35 points and 0.39 points for 5 mg/day and 10 mg/day of donepezil, respectively. These differences were statistically significant. There was no statistically significant difference between the two active treatments.

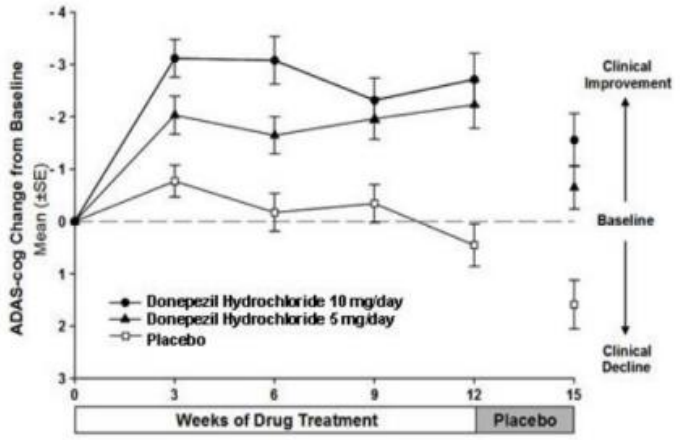
Figure 3. Frequency Distribution of CIBIC-plus Scores at Week 24



Fifteen-Week Study- In a study of 15 weeks duration, patients were randomized to receive single daily doses of placebo or either 5 mg/day or 10 mg/day of donepezil tablets for 12 weeks, followed by a 3-week placebo washout period. As in the 30-week study, to avoid acute cholinergic effects, the 10 mg/day treatment followed an initial 7-day treatment with 5 mg/day doses.

Effects on the ADAS-cog- Figure 4 illustrates the time course of the change from baseline in ADAS-cog scores for all three dose groups over the 15 weeks of the study. After 12 weeks of treatment, the differences in mean ADAS-cog change scores for the donepezil treated patients compared to the patients on placebo were 2.7 and 3.0 points each, for the 5 and 10 mg/day donepezil treatment groups, respectively. These differences were statistically significant. The effect size for the 10 mg/day group may appear to be slightly larger than that for 5 mg/day. However, the differences between active treatments were not statistically significant.

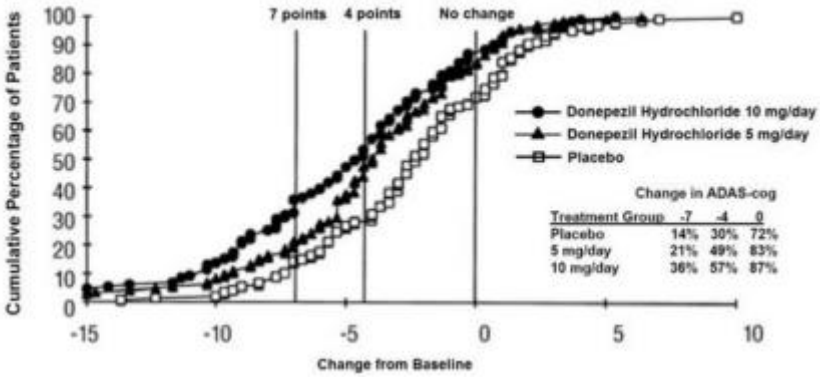
Figure 4. Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing the 15-week Study



Following 3 weeks of placebo washout, scores on the ADAS-cog for both the donepezil treatment groups increased, indicating that discontinuation of donepezil resulted in a loss of its treatment effect. The duration of this placebo washout period was not sufficient to characterize the rate of loss of the treatment effect, but the 30-week study demonstrated that treatment effects associated with the use of donepezil abate within 6 weeks of treatment discontinuation.

Figure 5 illustrates the cumulative percentages of patients from each of the three treatment groups who attained the measure of improvement in ADAS-cog score shown on the X-axis. The same three change scores (7-point and 4-point reductions from baseline or no change in score) as selected for the 30-week study have been used for this illustration. The percentages of patients achieving those results are shown in the inset table. As observed in the 30-week study, the curves demonstrate that patients assigned to either placebo or to donepezil have a wide range of responses, but that the donepezil treated patients are more likely to show greater improvements in cognitive performance.

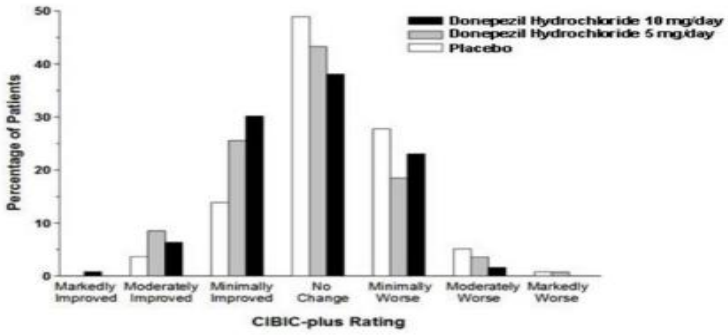
Figure 5. Cumulative Percentage of Patients with Specified Changes from Baseline ADAS-cog Scores. The Percentage of Randomized Patients Within Each Treatment Group Who Completed the Study were: Placebo 93%, 5mg/day 90% and 10mg/day 82%



Effects on the CIBIC-plus- Figure 6 is a histogram of the frequency distribution of CIBIC-plus scores attained by patients assigned to each of the three treatment groups who completed 12 weeks of treatment. The differences in mean scores for donepezil treated patients compared to the patients on placebo at Week 12 were 0.36 and 0.38 points for the 5 mg/day and 10 mg/day treatment groups, respectively. These differences were statistically

significant. In both studies, patient age, sex, and race were not found to predict the clinical outcome of donepezil treatment.

Figure 6. Frequency Distribution of CIBIC-plus Scores at Week 12



Moderate to Severe Alzheimer's Disease-

The effectiveness of donepezil in the treatment of patients with moderate to severe Alzheimer's disease was established in studies employing doses of 10 mg/day.

Swedish 6 Month Study (10 mg/day)- The effectiveness of donepezil as a treatment for severe Alzheimer's disease is demonstrated by the results of a randomized, double-blind, placebo-controlled clinical study conducted in Sweden (6-month study) in patients with probable or possible Alzheimer's disease diagnosed by NINCDS-ADRDA and DSM-IV criteria, MMSE: range of 1-10. Two hundred and forty-eight (248) patients with severe Alzheimer's disease were randomized to donepezil tablets or placebo. For patients randomized to donepezil, treatment was initiated at 5 mg once daily for 28 days and then increased to 10 mg once daily. At the end of the 6-month treatment period, 90.5% of the donepezil treated patients were receiving the 10 mg/day dose. The mean age of patients was 84.9 years, with a range of 59 to 99. Approximately 77% of patients were women, and 23% were men. Almost all patients were Caucasian. Probable Alzheimer's disease was diagnosed in the majority of the patients (83.6% of donepezil treated patients and 84.2% of placebo treated patients).

Study Outcome Measures- The effectiveness of treatment with donepezil was determined using a dual outcome assessment strategy that evaluated cognitive function using an instrument designed for more impaired patients and overall function through caregiver-rated assessment. This study showed that patients on donepezil experienced significant improvement on both measures compared to placebo. The ability of donepezil to improve cognitive performance was assessed with the Severe Impairment Battery (SIB). The SIB, a multi-item instrument, has been validated for the evaluation of cognitive function in patients with moderate to severe dementia. The SIB evaluates selective aspects of cognitive performance, including elements of memory, language, orientation, attention, praxis, visuospatial ability, construction, and social interaction. The SIB scoring range is from 0 to 100, with lower scores indicating greater cognitive impairment. Daily function was assessed using the Modified Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory for Severe Alzheimer's Disease (ADCS-ADL-severe). The ADCS-ADL-severe is derived from the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory, which is a comprehensive battery of ADL questions used to measure the functional capabilities of patients. Each ADL item is rated from the highest level of independent performance to complete loss. The ADCS-ADL-severe is a subset of 19 items, including ratings of the patient's ability to eat, dress, bathe, use the telephone, get around (or travel), and perform other activities of daily living; it has been validated for the assessment of patients with moderate to severe dementia. The ADCS-ADL-severe has a scoring range of 0 to 54, with the lower scores indicating greater functional impairment. The investigator performs the inventory by interviewing a caregiver, in this study a nurse staff member, familiar with the functioning of the patient.

Effects on the SIB- Figure 7 shows the time course for the change from baseline in SIB score for the two treatment groups over the 6 months of the study. At 6 months of treatment, the mean difference in the SIB change scores for donepezil treated patients compared to patients on placebo was 5.9 points. Donepezil treatment was statistically significantly superior to placebo.

Figure 7. Time Course of the Changes from Baseline in SIB Score for Patients Completing 6 months of Treatment

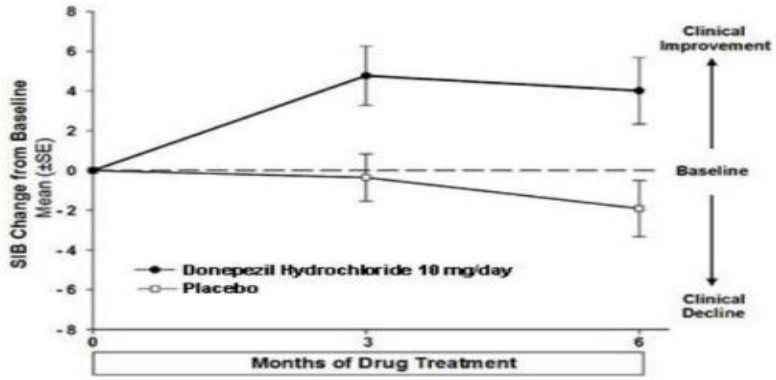
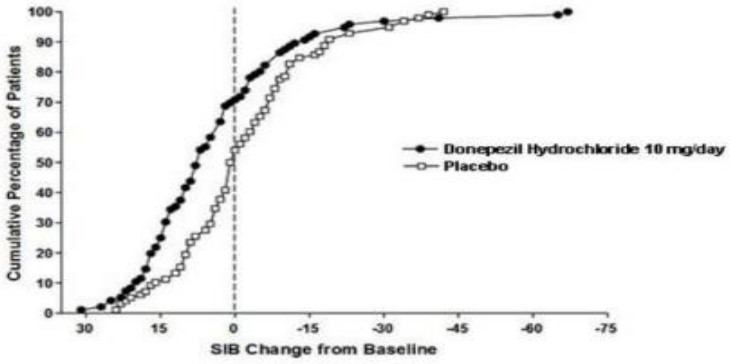


Figure 8 illustrates the cumulative percentages of patients from each of the two treatment groups who attained the measure of improvement in SIB score shown on the X-axis. While patients assigned both to donepezil and to placebo have a wide range of responses, the curves show that the donepezil group is more likely to show a greater improvement in cognitive performance.

Figure 8. Cumulative Percentage of Patients Completing 6 months of Doubled-blind Treatment with Particular Changes from Baseline in SIB Scores



Effects on the ADCS-ADL-severe- Figure 9 illustrates the time course for the change from baseline in ADCS-ADL-severe scores for patients in the two treatment groups over the 6 months of the study. After 6 months of treatment, the mean difference in the ADCS-ADL-severe change scores for donepezil treated patients compared to patients on placebo was 1.8 points. Donepezil treatment was statistically significantly superior to placebo.

Figure 9. Time Course of the Changes from Baseline in ADCS-ADL-Severe Score for Patients Completing 6 months of Treatment

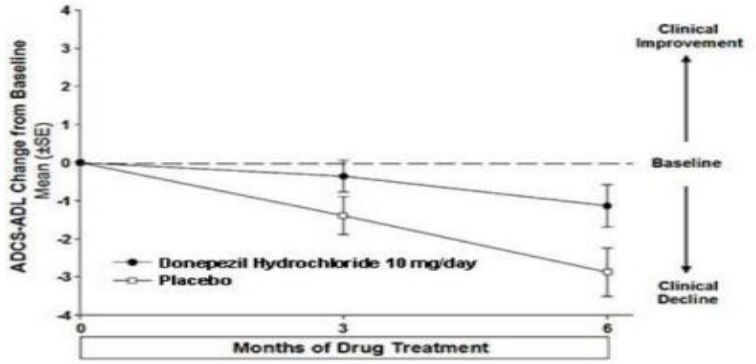
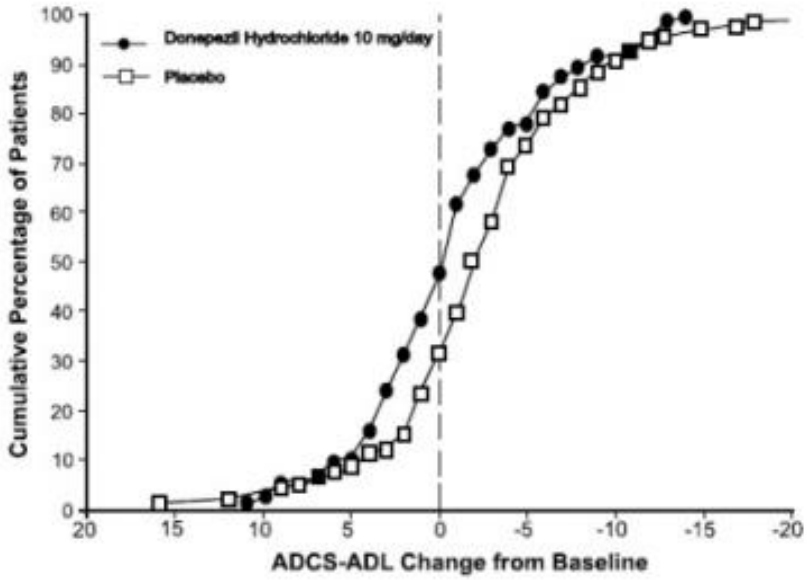


Figure 10 shows the cumulative percentages of patients from each treatment group with specified changes from baseline ADCS-ADL-severe scores. While both patients assigned to donepezil and placebo have a wide range of responses, the curves demonstrate that the donepezil group is more likely to show a smaller decline or an improvement.

Figure 10. Cumulative Percentage of Patients Completing 6 Months of Doubled-blind Treatment with Particular Changes from Baseline in ADCS-ADL-Severe Scores



Japanese 24-Week Study (10 mg/day)- In a study of 24 weeks duration conducted in Japan, 325 patients with severe Alzheimer's disease were randomized to doses of 5 mg/day or 10 mg/day of donepezil tablets, administered once daily, or placebo. Patients randomized to treatment with donepezil were to achieve their assigned doses by titration, beginning at 3 mg/day, and extending over a maximum of 6 weeks. Two hundred and forty-eight (248) patients completed the study, with similar proportions of patients completing the study in each treatment group. The primary efficacy measures for this study were the SIB and CIBIC-plus.

At 24 weeks of treatment, statistically significant treatment differences were observed between the 10 mg/day dose of donepezil and placebo on both the SIB and CIBIC-plus. The 5 mg/day dose of donepezil showed a statistically significant superiority to placebo on the SIB, but not on the CIBIC-plus.

Adhesion of Adlarity® Transdermal System-

Based on a clinical study in 85 subjects, each wearing one Adlarity® 5 mg/day on the back, 80 transdermal systems (94%) exhibited 80% or greater surface area adhesion at all timepoints evaluated (every 12 hours) throughout the 168-hour wear period. Based on a clinical study in 85 subjects, each wearing an Adlarity® 10 mg/day for 168 hours on the back for 4 consecutive weeks, 307 of 338 transdermal systems (91%) exhibited 80% or greater surface area adhesion at all timepoints evaluated. No full detachments were seen for any transdermal system applied. In a separate study, which assessed wear at different application sites (back, thigh, and buttock), at least 85% of the transdermal systems applied at every site exhibited 80% or greater surface area adhesion for the duration of wear. One full detachment on the back was noted in the study.

Safety

ADVERSE EVENTS

Most common adverse reactions (greater than 5% with donepezil tablets and twice the placebo rate) are nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, and anorexia.

WARNINGS & PRECAUTIONS

- Application-site reactions have occurred with Adlarity®. Allergic contact dermatitis should be suspected if application-site reactions spread beyond the size of the transdermal system, if there is evidence of a more intense local reaction (e.g., increasing erythema, edema, papules, vesicles), and/or if symptoms do not significantly improve within 48 hours after transdermal system removal.
- Cholinesterase inhibitors, including Adlarity®, are likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.
- Cholinesterase inhibitors, including Adlarity®, may have vagotonic effects on the sinoatrial and atrioventricular nodes manifesting as bradycardia or heart block.
- Adlarity®can cause vomiting. Patients should be observed closely at initiation of treatment and after dose increases.
- Patients should be monitored closely for symptoms of active or occult gastrointestinal (GI) bleeding, especially those at increased risk for developing ulcers.
- Cholinomimetics, including Adlarity®, may cause bladder outflow obstructions.
- Cholinomimetics, including Adlarity®, are believed to have some potential to cause generalized convulsions.
- Cholinesterase inhibitors, including Adlarity®, should be prescribed with caution to patients with a history of asthma or obstructive pulmonary disease.

CONTRAINDICATIONS

- Known hypersensitivity to donepezil or to piperidine derivative.
- History of allergic contact dermatitis with use of Adlarity®

Clinical Pharmacology

MECHANISMS OF ACTION

Donepezil 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 acetylcholinesterase. There is no evidence that donepezil alters the course of the underlying dementing process.

Dose & Administration

ADULTS

Initially, apply 1 patch (delivers 5 mg/day of donepezil) topically to the back (avoiding the spine) once every 7 days. If needed, the patch may be applied to the upper buttocks or upper outer thigh. Apply patch to healthy, intact skin with minimal hair. Wear for 7 days, then remove and apply new patch. Only apply 1 transdermal patch at a time. Rotate site of application and do not repeat location for at least 2 weeks after removal of patch. After 4 to 6 weeks of use, patch dose may be increased to 10 mg/day. When switching from oral donepezil to the transdermal patch, apply the first patch at the same time as the last oral dose. Patients taking a 5 mg once daily oral dose of donepezil may switch to the 5 mg/day patch. Patients taking either oral donepezil 5 mg/day for 4 to 6 weeks and who require a dose increase or those taking 10 mg/day may switch to the 10 mg/day patch.

PEDIATRICS

None

GERIATRICS

Refer to adult dosing

RENAL IMPAIRMENT

None

HEPATIC IMPAIRMENT

Although dosage adjustments are not required, patients with hepatic impairment should be closely monitored because donepezil is extensively metabolized in the liver.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Transdermal System: 5 mg/day and 10 mg/day.