DONEPEZIL HYDROCHLORIDE- donepezil hydrochloride tablet, film coated
Coupler LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DONEPEZIL HYDROCHLORIDE TABLETS safely and effectively. See full prescribing information for DONEPEZIL HYDROCHLORIDE TABLETS.

DONEPEZIL HYDROCHLORIDE tablets, for oral use
Initial U.S. Approval: 1996

INDICATIONS AND USAGE

Donepezil is an acetylcholinesterase inhibitor indicated for the treatment of dementia of the Alzheimer's type. Efficacy has been demonstrated in patients with mild, moderate, and severe Alzheimer's Disease (1)

DOSAGE AND ADMINISTRATION

- Mild to Moderate Alzheimer's Disease: 5 mg to 10 mg once daily (2.1)
- Moderate to Severe Alzheimer's Disease: 10 mg to 23 mg once daily (2.2)

DOSAGE FORMS AND STRENGTHS

- Tablets: 5 mg and 10 mg (3)

CONTRAINDICATIONS

Known hypersensitivity to donepezil hydrochloride or to piperidine derivatives (4)

WARNINGS AND PRECAUTIONS

- Cholinesterase inhibitors are likely to exaggerate succinylcholine-type muscle relaxation during anesthesia (5.1)
- Cholinesterase inhibitors may have vagotonic effects on the sinoatrial and atrioventricular nodes manifesting as bradycardia or heart block (5.2)
- Donepezil hydrochloride can cause vomiting. Patients should be observed closely at initiation of treatment and after dose increases (5.3)
- Patients should be monitored closely for symptoms of active or occult gastrointestinal (GI) bleeding, especially those at increased risk for developing ulcers (5.4)
- The use of donepezil hydrochloride in a dose of 23 mg once daily is associated with weight loss (5.5)
- Cholinomimetics may cause bladder outflow obstructions (5.6)
- Cholinomimetics are believed to have some potential to cause generalized convulsions (5.7)
- Cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease (5.8)

ADVERSE REACTIONS

Most common adverse reactions in clinical studies of donepezil hydrochloride are nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, and anorexia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Rising Pharma Holdings, Inc. at 1(844) 874-7464 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

- Cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications (7.1)
- A synergistic effect may be expected with concomitant administration of succinylcholine, similar neuromuscular blocking agents, or cholinergic agonists (7.2)

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm (8.1)

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

Revised: 3/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Donepezil hydrochloride tablets are indicated for the treatment of dementia of the Alzheimer’s type. Efficacy has been demonstrated in patients with mild, moderate, and severe Alzheimer’s disease.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing in Mild to Moderate Alzheimer's Disease

The recommended starting dosage of donepezil hydrochloride tablets is 5 mg administered once per day in the evening, just prior to retiring. The maximum recommended dosage of donepezil hydrochloride tablets in patients with mild to moderate Alzheimer’s disease is 10 mg per day. A dose of 10 mg should not be administered until patients have been on a daily dose of 5 mg for 4 to 6 weeks.

2.2 Dosing in Moderate to Severe Alzheimer's Disease

The recommended starting dosage of donepezil hydrochloride tablets is 5 mg administered once per day in the evening, just prior to retiring. The maximum recommended dosage of donepezil hydrochloride tablets in patients with moderate to severe Alzheimer’s disease is 23 mg per day. A dose of 10 mg should not be administered until patients have been on a daily dose of 5 mg for 4 to 6 weeks. A dose of 23 mg per day should not be administered until patients have been on a daily dose of 10 mg for at least 3 months.

2.3 Administration Information

Donepezil hydrochloride tablets should be taken in the evening, just prior to retiring.

Donepezil hydrochloride tablets can be taken with or without food.

The donepezil hydrochloride 23 mg tablet should not be split, crushed, or chewed.

3 DOSAGE FORMS AND STRENGTHS

Donepezil hydrochloride tablets USP are supplied as film-coated, round tablets containing 5 mg, and 10 mg of donepezil hydrochloride.

- The 5 mg tablets are white to off-white, circular, biconvex, film-coated tablets debossed with ‘X’ on one side and ‘11’ on the other side.
- The 10 mg tablets are yellow colored, circular, biconvex, film-coated tablets debossed with ‘X’ on one side and ‘12’ on the other side.

4 CONTRAINDICATIONS

Donepezil hydrochloride tablets are contraindicated in patients with known

hypersensitivity to donepezil hydrochloride or to piperidine derivatives.

5 WARNINGS AND PRECAUTIONS

5.1 Anesthesia

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

5.2 Cardiovascular Conditions

Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on the sinoatrial and atrioventricular nodes. This effect may manifest as bradycardia or heart block in patients both with and without known underlying cardiac conduction abnormalities. Syncopal episodes have been reported in association with the use of donepezil hydrochloride.

5.3 Nausea and Vomiting

Donepezil hydrochloride, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea, and vomiting. These effects, when they occur, appear more frequently with the 10 mg/day dose than with the 5 mg/day dose, and more frequently with the 23 mg dose than with the 10 mg dose. Specifically, in a controlled trial that compared a dose of 23 mg/day to 10 mg/day in patients who had been treated with donepezil 10 mg/day for at least three months, the incidence of nausea in the 23 mg group was markedly greater than in the patients who continued on 10 mg/day (11.8% vs. 3.4%, respectively), and the incidence of vomiting in the 23 mg group was markedly greater than in the 10 mg group (9.2% vs. 2.5%, respectively). The percent of patients who discontinued treatment due to vomiting in the 23 mg group was markedly higher than in the 10 mg group (2.9% vs. 0.4%, respectively).

Although in most cases, these effects have been transient, sometimes lasting one to three weeks, and have resolved during continued use of donepezil hydrochloride, patients should be observed closely at the initiation of treatment and after dose increases.

5.4 Peptic Ulcer Disease and GI Bleeding

Through their primary 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 anti-inflammatory drugs (NSAIDs). Clinical studies of donepezil hydrochloride in a dose of 5 mg/day to 10 mg/day have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. Results of a controlled clinical study with 23 mg/day showed an

increase, relative to 10 mg/day, in the incidence of peptic ulcer disease (0.4% vs. 0.2%) and gastrointestinal bleeding from any site (1.1% vs. 0.6%).

5.5 Weight Loss

Weight loss was reported as an adverse reaction in 4.7% of patients assigned to donepezil hydrochloride in a dose of 23 mg/day compared to 2.5% of patients assigned to 10 mg/day. Compared to their baseline weights, 8.4% of patients taking 23 mg/day were found to have a weight decrease of ≥ 7% by the end of the study, while 4.9% of patients taking 10 mg/day were found to have weight loss of ≥ 7% at the end of the study.

5.6 Genitourinary Conditions

Although not observed in clinical trials of donepezil hydrochloride, cholinomimetics may cause bladder outflow obstruction.

5.7 Neurological Conditions: Seizures

Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a manifestation of Alzheimer's disease.

5.8 Pulmonary Conditions

Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling:

- Cardiovascular Conditions *[see Warnings and Precautions (5.2)]*
- Nausea and Vomiting *[see Warnings and Precautions (5.3)]*
- Peptic Ulcer Disease and GI Bleeding *[see Warnings and Precautions (5.4)]*
- Weight Loss *[see Warnings and Precautions (5.5)]*
- Genitourinary Conditions *[see Warnings and Precautions (5.6)]*
- Neurological Conditions: Seizures *[see Warnings and Precautions (5.7)]*
- Pulmonary Conditions *[see Warnings and Precautions (5.8)]*

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.

Donepezil hydrochloride has been administered to over 1,700 individuals during clinical

trials worldwide. Approximately 1200 of these patients have been treated for at least 3 months and more than 1,000 patients have been treated for at least 6 months. Controlled and uncontrolled trials in the United States included approximately 900 patients. In regards to the highest dose of 10 mg/day, this population includes 650 patients treated for 3 months, 475 patients treated for 6 months, and 116 patients treated for over 1 year. The range of patient exposure is from 1 to 1,214 days.

Mild to Moderate Alzheimer's Disease

Adverse Reactions Leading to Discontinuation

The rates of discontinuation from controlled clinical trials of donepezil hydrochloride due to adverse reactions for the donepezil hydrochloride 5 mg/day treatment groups were comparable to those of placebo treatment groups at approximately 5%. The rate of discontinuation of patients who received 7-day escalations from 5 mg/day to 10 mg/day was higher at 13%.

The most common adverse reactions leading to discontinuation, defined as those occurring in at least 2% of patients and at twice or more the incidence seen in placebo patients, are shown in Table 1.

Table 1. Most Common Adverse Reactions Leading to Discontinuation in Patients with Mild to Moderate Alzheimer's Disease

Adverse Reaction	Placebo (n=355) %	5 mg/day Donepezil Hydrochloride (n=350) %	10 mg/day Donepezil Hydrochloride (n=315) %
Nausea	1	1	3
Diarrhea	0	<1	3
Vomiting	<1	<1	2

Most Common Adverse Reactions

The most common adverse reactions, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and twice the placebo rate, are largely predicted by donepezil hydrochloride's cholinomimetic effects. These include nausea, diarrhea, insomnia, vomiting, muscle cramp, fatigue, and anorexia. These adverse reactions were often transient, resolving during continued donepezil hydrochloride treatment without the need for dose modification.

There is evidence to suggest that the frequency of these common adverse reactions may be affected by the rate of titration. An open-label study was conducted with 269

patients who received placebo in the 15- and 30-week studies. These patients were titrated to a dose of 10 mg/day over a 6-week period. The rates of common adverse reactions were lower than those seen in patients titrated to 10 mg/day over one week in the controlled clinical trials and were comparable to those seen in patients on 5 mg/day.

See Table 2 for a comparison of the most common adverse reactions following one and six week titration regimens.

Table 2. Comparison of Rates of Adverse Reactions in Mild to Moderate Patients Titrated to 10 mg/day over 1 and 6 Weeks

Adverse Reaction	No titration		One week titration	Six week titration
	Placebo (n=315) %	5 mg/day (n=311) %	10 mg/day (n=315) %	10 mg/day (n=269) %
Nausea	6	5	19	6
Diarrhea	5	8	15	9
Insomnia	6	6	14	6
Fatigue	3	4	8	3
Vomiting	3	3	8	5
Muscle cramps	2	6	8	3
Anorexia	2	3	7	3

Table 3 lists adverse reactions that occurred in at least 2% of patients in pooled placebo-controlled trials who received either donepezil hydrochloride 5 mg or 10 mg and for which the rate of occurrence was greater for patients treated with donepezil hydrochloride than with placebo. In general, adverse reactions occurred more frequently in female patients and with advancing age.

Table 3. Adverse Reactions in Pooled Placebo-Controlled Clinical Trials in Mild to Moderate Alzheimer's Disease

Adverse Reaction	Placebo (n=355) %	Donepezil Hydrochloride (n=747) %
Percent of Patients with any Adverse Reaction	**72**	**74**
Nausea	6	11
Diarrhea	5	10
Headache	9	10
Insomnia	6	9
Pain, various locations	8	9
Dizziness	6	8
Accident	6	7

Muscle Cramps	2	6
Fatigue	3	5
Vomiting	3	5
Anorexia	2	4
Ecchymosis	3	4
Abnormal Dreams	0	3
Depression	<1	3
Weight Loss	1	3
Arthritis	1	2
Frequent Urination	1	2
Somnolence	<1	2
Syncope	1	2

Severe Alzheimer's Disease (Donepezil hydrochloride 5 mg/day and 10 mg/day)

Donepezil hydrochloride has been administered to over 600 patients with severe Alzheimer's disease during clinical trials of at least 6 months duration, including three double-blind, placebo-controlled trials, two of which had an open label extension.

Adverse Reactions Leading to Discontinuation

The rates of discontinuation from controlled clinical trials of donepezil hydrochloride due to adverse reactions for the donepezil hydrochloride patients were approximately 12% compared to 7% for placebo patients. The most common adverse reactions leading to discontinuation, defined as those occurring in at least 2% of donepezil hydrochloride patients and at twice or more the incidence seen in placebo, were anorexia (2% vs. 1% placebo), nausea (2% vs. <1% placebo), diarrhea (2% vs. 0% placebo), and urinary tract infection (2% vs. 1% placebo).

Most Common Adverse Reactions

The most common adverse reactions, defined as those occurring at a frequency of at least 5% in patients receiving donepezil hydrochloride and at twice or more the placebo rate, are largely predicted by donepezil hydrochloride's cholinomimetic effects. These include diarrhea, anorexia, vomiting, nausea, and ecchymosis. These adverse reactions were often transient, resolving during continued donepezil hydrochloride treatment without the need for dose modification.

Table 4 lists adverse reactions that occurred in at least 2% of patients in pooled placebo-controlled trials who received donepezil hydrochloride 5 mg or 10 mg and for which the rate of occurrence was greater for patients treated with donepezil hydrochloride than with placebo.

Table 4. Adverse Reactions in Pooled Controlled Clinical Trials in Severe Alzheimer's Disease

Body System/Adverse Reaction	**Placebo (n=392)**	**Donepezil Hydrochloride**

	(n=392) %	(n=501) %
Percent of Patients with any Adverse Reaction	**73**	**81**
Accident	12	13
Infection	9	11
Diarrhea	4	10
Anorexia	4	8
Vomiting	4	8
Nausea	2	6
Insomnia	4	5
Ecchymosis	2	5
Headache	3	4
Hypertension	2	3
Pain	2	3
Back Pain	2	3
Eczema	2	3
Hallucinations	1	3
Hostility	2	3
Increase in Creatine Phosphokinase	1	3
Nervousness	2	3
Fever	1	2
Chest Pain	<1	2
Confusion	1	2
Dehydration	1	2
Depression	1	2
Dizziness	1	2
Emotional Lability	1	2
Hemorrhage	1	2
Hyperlipemia	<1	2
Personality Disorder	1	2
Somnolence	1	2
Syncope	1	2
Urinary Incontinence	1	2

Moderate to Severe Alzheimer's Disease (Donepezil Hydrochloride 23 mg/day)

Donepezil hydrochloride 23 mg/day has been administered to over 1300 individuals globally in clinical trials. Approximately 1050 of these patients have been treated for at least three months and more than 950 patients have been treated for at least six months. The range of patient exposure was from 1 to over 500 days.

Adverse Reactions Leading to Discontinuation

The rate of discontinuation from a controlled clinical trial of donepezil hydrochloride 23 mg/day due to adverse reactions was higher (19%) than for the 10 mg/day treatment group (8%). The most common adverse reactions leading to discontinuation, defined as those occurring in at least 1% of patients and greater than those occurring with 10

mg/day are shown in Table 5.

Table 5. Most Common Adverse Reactions Leading to Discontinuation in Patients with Moderate to Severe Alzheimer's Disease

Adverse Reaction	23 mg/dayDonepezil Hydrochloride (n=963) %	10 mg/dayDonepezil Hydrochloride (n=471) %
Vomiting	3	0
Diarrhea	2	0
Nausea	2	0
Dizziness	1	0

The majority of discontinuations due to adverse reactions in the 23 mg group occurred during the first month of treatment.

Most Common Adverse Reactions with Donepezil Hydrochloride 23 mg/day

The most common adverse reactions, defined as those occurring at a frequency of at least 5%, include nausea, diarrhea, vomiting, and anorexia.

Table 6 lists adverse reactions that occurred in at least 2% of patients who received 23 mg/day of donepezil hydrochloride and at a higher frequency than those receiving 10 mg/day of donepezil hydrochloride in a controlled clinical trial that compared the two doses. In this study, there were no important differences in the type of adverse reactions in patients taking donepezil hydrochloride with or without memantine.

Table 6. Adverse Reactions in a Controlled Clinical Trial in Moderate to Severe Alzheimer's Disease

Adverse Reaction	23 mg/dayDonepezil Hydrochloride (n=963) %	10 mg/dayDonepezil Hydrochloride (n=471) %
Percent of Patients with any Adverse Reaction	74	64
Nausea	12	3
Vomiting	9	3
Diarrhea	8	5
Anorexia	5	2
Dizziness	5	3
Weight Loss	5	3
Headache	4	3
Insomnia	3	2
Urinary Incontinence	3	1

Asthenia	2	1
Contusion	2	0
Fatigue	2	1
Somnolence	2	1

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of donepezil hydrochloride. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Abdominal pain, agitation, aggression, cholecystitis, confusion, convulsions, hallucinations, heart block (all types), hemolytic anemia, hepatitis, hyponatremia, neuroleptic malignant syndrome, pancreatitis, rash, rhabdomyolysis, QTc prolongation, and torsade de pointes.

7 DRUG INTERACTIONS

7.1 Use with Anticholinergics

Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

7.2 Use with Cholinomimetics and Other Cholinesterase Inhibitors

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

Risk Summary

There are no adequate data on the developmental risks associated with the use of donepezil hydrochloride in pregnant women. In animal studies, developmental toxicity was not observed when donepezil was administered to pregnant rats and rabbits during organogenesis, but administration to rats during the latter part of pregnancy and throughout lactation resulted in increased stillbirths and decreased offspring survival at clinically relevant doses *[see Data]*. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively. The background risks of major birth defects and miscarriage for the indicated population are unknown.

Data

Animal Data

Oral administration of donepezil to pregnant rats and rabbits during the period of organogenesis did not produce any teratogenic effects at doses up to 16 mg/kg/day (approximately 6 times the maximum recommended human dose [MRHD] of 23 mg/day on a mg/m ^{2}basis) and 10 mg/kg/day (approximately 7 times the MRHD on a mg/m ^{2}basis), respectively. Oral administration of donepezil (1, 3, 10 mg/kg/day) to rats during late gestation and throughout lactation to weaning produced an increase in stillbirths and reduced offspring survival through postpartum day 4 at the highest dose. The no-effect dose of 3 mg/kg/day is approximately equal to the MRHD on a mg/m ^{2}basis.

8.2 Lactation

Risk Summary

There are no data on the presence of donepezil or its metabolites in human milk, the effects on the breastfed infant, or on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for donepezil hydrochloride and any potential adverse effects on the breastfed infant from donepezil hydrochloride or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Alzheimer's disease is a disorder occurring primarily in individuals over 55 years of age. The mean age of patients enrolled in the clinical studies with donepezil hydrochloride was 73 years; 80% of these patients were between 65 and 84 years old, and 49% of patients were at or above the age of 75. The efficacy and safety data presented in the clinical trials section were obtained from these patients. There were no clinically significant differences in most adverse reactions reported by patient groups ≥ 65 years old and < 65 years old.

8.6 Lower Weight Individuals

In the controlled clinical trial, among patients in the donepezil hydrochloride 23 mg treatment group, those patients weighing < 55 kg reported more nausea, vomiting, and decreased weight than patients weighing 55 kg or more. There were more withdrawals due to adverse reactions as well. This finding may be related to higher plasma exposure associated with lower weight.

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. 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. Tertiary anticholinergics such as atropine may be used as an antidote for donepezil hydrochloride overdosage. Intravenous atropine sulfate titrated to effect is recommended: an initial dose of 1 to 2 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether donepezil hydrochloride and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration).

Dose-related signs of toxicity in animals included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, tremors, fasciculation, and lower body surface temperature.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Current theories on the pathogenesis of the cognitive signs and symptoms of Alzheimer’s disease attribute some of them to a deficiency of cholinergic neurotransmission.

Donepezil hydrochloride 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.

12.3 Pharmacokinetics

Pharmacokinetics of donepezil are linear over a dose range of 1 to 10 mg given once daily. The rate and extent of absorption of donepezil hydrochloride tablets are not influenced by food.

Based on population pharmacokinetic analysis of plasma donepezil concentrations measured in patients with Alzheimer’s disease, following oral dosing, peak plasma concentration is achieved for donepezil hydrochloride 23 mg tablets in approximately 8 hours, compared with 3 hours for donepezil hydrochloride 10 mg tablets. Peak plasma concentrations were about 2-fold higher for donepezil hydrochloride 23 mg tablets than donepezil hydrochloride 10 mg tablets.

The elimination half life of donepezil is about 70 hours, and the mean apparent plasma

clearance (Cl/F) is 0.13 to 0.19 L/hr/kg. Following multiple dose administration, donepezil accumulates in plasma by 4 to 7 fold, and steady state is reached within 15 days. The steady state volume of distribution is 12 to 16 L/kg. Donepezil is approximately 96% bound to human plasma proteins, mainly to albumins (about 75%) and alpha $_1$- acid glycoprotein (about 21%) over the concentration range of 2 to 1000 ng/mL.

Donepezil is both excreted in the urine intact and extensively metabolized to four major metabolites, two of which are known to be active, and a number of minor metabolites, not all of which have been identified. Donepezil is metabolized by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation. Following administration of ^{14}C-labeled donepezil, plasma radioactivity, expressed as a percent of the administered dose, was present primarily as intact donepezil (53%) and as 6-O-desmethyl donepezil (11%), which has been reported to inhibit AChE to the same extent as donepezil *in vitro* and was found in plasma at concentrations equal to about 20% of donepezil. Approximately 57% and 15% of the total radioactivity was recovered in urine and feces, respectively, over a period of 10 days, while 28% remained unrecovered, with about 17% of the donepezil dose recovered in the urine as unchanged drug. Examination of the effect of CYP2D6 genotype in Alzheimer's patients showed differences in clearance values among CYP2D6 genotype subgroups. When compared to the extensive metabolizers, poor metabolizers had a 31.5% slower clearance and ultra-rapid metabolizers had a 24% faster clearance.

Hepatic Disease
In a study of 10 patients with stable alcoholic cirrhosis, the clearance of donepezil hydrochloride was decreased by 20% relative to 10 healthy age- and sex-matched subjects.

Renal Disease
In a study of 11 patients with moderate to severe renal impairment (Cl_C< 18 mL/min/1.73 m ^{2}) the clearance of donepezil hydrochloride did not differ from 11 age- and sex-matched healthy subjects.

Age
No formal pharmacokinetic study was conducted to examine age-related differences in the pharmacokinetics of donepezil hydrochloride. Population pharmacokinetic analysis suggested that the clearance of donepezil in patients decreases with increasing age. When compared with 65-year old subjects, 90-year old subjects have a 17% decrease in clearance, while 40-year old subjects have a 33% increase in clearance. The effect of age on donepezil clearance may not be clinically significant.

Gender and Race
No specific pharmacokinetic study was conducted to investigate the effects of gender and race on the disposition of donepezil hydrochloride. However, retrospective pharmacokinetic analysis and population pharmacokinetic analysis of plasma donepezil concentrations measured in patients with Alzheimer's disease indicates that gender and race (Japanese and Caucasians) did not affect the clearance of donepezil hydrochloride to an important degree.

Body Weight

There was a relationship noted between body weight and clearance. Over the range of

body weight from 50 kg to 110 kg, clearance increased from 7.77 L/h to 14.04 L/h, with a value of 10 L/hr for 70 kg individuals.

Drug Interactions

Effect of Donepezil Hydrochloride on the Metabolism of Other Drugs

No *in vivo* clinical trials have investigated the effect of donepezil hydrochloride on the clearance of drugs metabolized by CYP 3A4 (e.g., cisapride, terfenadine) or by CYP 2D6 (e.g., imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean K_i about 50 to 130 μM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference. Based on *in vitro* studies, donepezil shows little or no evidence of direct inhibition of CYP2B6, CYP2C8, and CYP2C19 at clinically relevant concentrations.

Whether donepezil hydrochloride has any potential for enzyme induction is not known. Formal pharmacokinetic studies evaluated the potential of donepezil hydrochloride for interaction with theophylline, cimetidine, warfarin, digoxin, and ketoconazole. No effects of donepezil hydrochloride on the pharmacokinetics of these drugs were observed.

Effect of Other Drugs on the Metabolism of Donepezil Hydrochloride

Ketoconazole and quinidine, strong inhibitors of CYP450 3A and 2D6, respectively, inhibit donepezil metabolism *in vitro*. Whether there is a clinical effect of quinidine is not known. Population pharmacokinetic analysis showed that in the presence of concomitant CYP2D6 inhibitors donepezil AUC was increased by approximately 17% to 20% in Alzheimer's disease patients taking donepezil hydrochloride 10 mg and 23 mg. This represented an average effect of weak, moderate, and strong CYP2D6 inhibitors. In a 7-day crossover study in 18 healthy volunteers, ketoconazole (200 mg q.d.) increased mean donepezil (5 mg q.d.) concentrations (AUC $_{0\text{-}24}$ and C_{max}) by 36%. The clinical relevance of this increase in concentration is unknown.

Inducers of CYP 3A (e.g., phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of donepezil hydrochloride.

Formal pharmacokinetic studies demonstrated that the metabolism of donepezil hydrochloride is not significantly affected by concurrent administration of digoxin or cimetidine.

An *in vitro* study showed that donepezil was not a substrate of P-glycoprotein.

Drugs Highly Bound to Plasma Proteins

Drug displacement studies have been performed *in vitro* between this highly bound drug (96%) and other drugs such as furosemide, digoxin, and warfarin. Donepezil

hydrochloride at concentrations of 0.3 to 10 micrograms/mL did not affect the binding of furosemide (5 micrograms/mL), digoxin (2 ng/mL), and warfarin (3 micrograms/mL) to human albumin. Similarly, the binding of donepezil hydrochloride to human albumin was not affected by furosemide, digoxin, and warfarin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenic potential was obtained in an 88-week carcinogenicity study of donepezil conducted in mice at oral doses up to 180 mg/kg/day (approximately 40 times the maximum recommended human dose [MRHD] of 23 mg/day on a mg/m ^{2}basis), or in a 104-week carcinogenicity study in rats at oral doses up to 30 mg/kg/day (approximately 13 times the MRHD on a mg/m ^{2}basis).

Donepezil was negative in a battery of genotoxicity assays (*in vitro*bacterial reverse mutation, *in vitro*mouse lymphoma *tk*, *in vitro*chromosomal aberration, and *in vivo*mouse micronucleus).

Donepezil had no effect on fertility in rats at oral doses up to 10 mg/kg/day (approximately 4 times the MRHD on a mg/m ^{2}basis) when administered to males and females prior to and during mating and continuing in females through implantation.

13.2 Animal Toxicology and/or Pharmacology

In an acute dose neurotoxicity study in female rats, oral administration of donepezil and memantine in combination resulted in increased incidence, severity, and distribution of neurodegeneration compared with memantine alone. The no-effect levels of the combination were associated with clinically relevant plasma donepezil and memantine levels.

The relevance of this finding to humans is unknown.

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Donepezil Hydrochloride Tablets USP

Supplied as film-coated, round tablets containing 5 mg, and 10 mg of donepezil hydrochloride.

Donepezil Hydrochloride Tablets USP, 5 mgare white to off-white, circular, biconvex, film-coated tablets debossed with ‘X’ on one side and ‘11’ on the other side.

Bottles of 30	NDC 16571-778-03
Bottles of 90	NDC 16571-778-09

Bottles of 500	NDC 16571-778-50
Bottles of 1,000	NDC 16571-778-10

Donepezil Hydrochloride Tablets USP, 10 mg are yellow colored, circular, biconvex, film-coated tablets debossed with ‘X’ on one side and ‘12’ on the other side.

Bottles of 30	NDC 16571-779-03
Bottles of 90	NDC 16571-779-09
Bottles of 500	NDC 16571-779-50
Bottles of 1,000	NDC 16571-779-10

Storage

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Instruct patients and caregivers to take donepezil hydrochloride only once per day, as prescribed.

Instruct patients and caregivers that donepezil hydrochloride can be taken with or without food. Donepezil hydrochloride 23 mg tablets should be swallowed whole without the tablets being split, crushed or chewed.

Advise patients and caregivers that donepezil hydrochloride may cause nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, and decreased appetite.

Advise patients to notify their healthcare provider if they are pregnant or plan to become pregnant.

Distributed by:
Rising Pharma Holdings, Inc.
East Brunswick, NJ 08816

Made in India

Code: TS/DRUGS/19/1993

Issued: 03/2021

PATIENT PACKAGE INSERT

Donepezil Hydrochloride Tablets USP

(doe nep' e zil hye'' droe klor' ide)

Read this Patient Information that comes with donepezil hydrochloride tablets before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about Alzheimer's disease or treatment for it. If you have questions, ask the doctor or pharmacist.

What are donepezil hydrochloride tablets?

Donepezil hydrochloride comes as donepezil hydrochloride film-coated tablets in dosage strengths of 5 mg, and 10 mg.

Donepezil hydrochloride tablets are a prescription medicine to treat mild, moderate, and severe Alzheimer's disease. Donepezil hydrochloride tablets can help with mental function and with doing daily tasks. Donepezil hydrochloride tablets do not work the same in all people. Some people may:

- Seem much better
- Get better in small ways or stay the same
- Get worse over time but slower than expected
- Not change and then get worse as expected

Donepezil hydrochloride tablets do not cure Alzheimer's disease. All patients with Alzheimer's disease get worse over time, even if they take donepezil hydrochloride tablets.

Donepezil hydrochloride tablets have not been approved as a treatment for any medical condition in children.

Who should not take donepezil hydrochloride tablets?

Do not take donepezil hydrochloride tablets if you are allergic to any of the ingredients in donepezil hydrochloride tablets or to medicines that contain piperidines. Ask your doctor if you are not sure. See the end of this leaflet for a list of ingredients in donepezil hydrochloride tablets.

What should I tell my doctor before taking donepezil hydrochloride tablets?

Tell the doctor about all of your present or past health problems and conditions. Include:

- Any heart problems including problems with irregular, slow, or fast heartbeats
- Asthma or lung problems
- A seizure
- Stomach ulcers
- Difficulty passing urine
- Liver or kidney problems
- Trouble swallowing tablets

- Present pregnancy or plans to become pregnant. It is not known if donepezil hydrochloride tablets can harm an unborn baby.
- Present breast-feeding. It is not known if donepezil hydrochloride passes into breast milk. Talk to your doctor about the best way to feed your baby if you take donepezil hydrochloride tablets.

Tell the doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal products. Donepezil hydrochloride tablets and other medicines may affect each other.

Be particularly sure to tell the doctor if you take aspirin or medicines called nonsteroidal anti-inflammatory drugs (NSAIDs). There are many NSAID medicines, both prescription and non-prescription. Ask the doctor or pharmacist if you are not sure if any of your medicines are NSAIDs. Taking NSAIDs and donepezil hydrochloride tablets together may make you more likely to get stomach ulcers.

Donepezil hydrochloride tablets taken with certain medicines used for anesthesia may cause side effects. Tell the responsible doctor or dentist that you take donepezil hydrochloride tablets before you have:

- surgery
- medical procedures
- dental surgery or procedures.

Know the medicines that you take. Keep a list of all your medicines. Show it to your doctor or pharmacist before you start a new medicine.

How should you take donepezil hydrochloride tablets?

- Take donepezil hydrochloride tablets exactly as prescribed by the doctor. Do not stop donepezil hydrochloride tablets or change the dose yourself. Talk with your doctor first.
- Take donepezil hydrochloride tablets one time each day. Donepezil hydrochloride tablets can be taken with or without food.
- Donepezil hydrochloride tablets 23 mg should be swallowed whole. Do not split, crush, or chew the tablets.
- If you miss a dose of donepezil hydrochloride tablets, just wait. Take only the next dose at the usual time. Do not take 2 doses at the same time.
- If donepezil hydrochloride tablets are missed for 7 days or more, talk with your doctor before starting again.
- If you take too much donepezil hydrochloride at one time, call your doctor or poison control center, or go to the emergency room right away.

What are the possible side effects of donepezil hydrochloride tablets?

Donepezil hydrochloride tablets may cause the following serious side effects:

- slow heartbeat and fainting. This happens more often in people with heart problems. Call your doctor right away if you feel faint or lightheaded while taking donepezil hydrochloride tablets.
- more stomach acid. This raises the chance of ulcers and bleeding, especially when taking donepezil hydrochloride tablets 23 mg. The risk is higher for people who have

had ulcers, or take aspirin or other NSAIDs.
- worsening of lung problems in people with asthma or other lung disease.
- seizures.
- difficulty passing urine.

Call your doctor *right away* if you have:
- fainting.
- heartburn or stomach pain that is new or won't go away.
- nausea or vomiting, blood in the vomit, dark vomit that looks like coffee grounds.
- bowel movements or stools that look like black tar.
- new or worse asthma or breathing problems.
- seizures.
- difficulty passing urine.

The most common side effects of donepezil hydrochloride tablets are:
- nausea
- diarrhea
- not sleeping well
- vomiting
- muscle cramps
- feeling tired
- not wanting to eat

These side effects may get better after you take donepezil hydrochloride tablets for a while. This is not a complete list of side effects with donepezil hydrochloride tablets. 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 donepezil hydrochloride tablets be stored?

Store donepezil hydrochloride tablets at room temperature between 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F).

Keep donepezil hydrochloride tablets and all medicines out of the reach of children.

General information about donepezil hydrochloride tablets

Medicines are sometimes prescribed for conditions that are not mentioned in this Patient Information Leaflet. Do not use donepezil hydrochloride tablets for a condition for which it was not prescribed. Do not give donepezil hydrochloride tablets to other people, even if they have the same symptoms or condition. It may harm them.

This leaflet summarizes the most important information about donepezil hydrochloride tablets. If you would like more information, talk with your doctor. You can ask your

pharmacist or doctor for information about donepezil hydrochloride tablets that is written for health professionals. For more information, call Rising Pharma Holdings, Inc. at 1(844) 874-7464.

What are the ingredients in donepezil hydrochloride tablets?

Active ingredient:donepezil hydrochloride

Inactive ingredients:hypromellose, lactose monohydrate, low substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, pregelatinized starch (maize), talc, and titanium dioxide. In addition, the 10 mg tablets also contain yellow iron oxide.

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Made in India

Code: TS/DRUGS/19/1993

Issued: 03/2021

DONEPEZIL HYDROCHLORIDE

donepezil hydrochloride tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:67046-1457(NDC:16571-779)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
DONEPEZIL HYDROCHLORIDE (UNII: 3O2T2PJ89D) (DONEPEZIL - UNII:8SSC91326P)	DONEPEZIL HYDROCHLORIDE	10 mg

Inactive Ingredients

Ingredient Name	Strength
HYPROMELLOSE 2910 (6 MPA.S) (UNII: 0WZ8WG20P6)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
LOW-SUBSTITUTED HYDROXYPROPYL CELLULOSE, UNSPECIFIED (UNII: 2165RE0K14)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POLYETHYLENE GLYCOL 6000 (UNII: 30IQX730WE)	
STARCH, CORN (UNII: O8232NY3SJ)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	

Product Characteristics

Color	yellow	**Score**	no score
Shape	ROUND (Biconvex)	**Size**	9mm
Flavor		**Imprint Code**	X;12
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:67046-1457-3	30 in 1 BLISTER PACK; Type 0: Not a Combination Product	11/25/2024	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090056	11/25/2024	

Labeler - Coupler LLC (119003108)

Establishment

Name	Address	ID/FEI	Business Operations
Coupler LLC		119003108	repack(67046-1457)

Revised: 11/2024 Coupler LLC