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

NAMZARIC (memantine and donepezil hydrochlorides) extended-release capsules, for oral use
Initial U.S. Approval: 2014

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	07/2016
Dosage and Administration (2.1, 2.3)	07/2016

---------- INDICATIONS AND USAGE----------

NAMZARIC is a combination of memantine hydrochloride, an NMDA receptor antagonist, and donepezil hydrochloride, an acetylcholinesterase inhibitor, indicated for the treatment of moderate to severe dementia of the Alzheimer's type in patients stabilized on 10 mg of donepezil hydrochloride once daily. (1)

----------DOSAGE AND ADMINISTRATION----------

- For patients on donepezil hydrochloride 10 mg only, the recommended starting dose of NAMZARIC is 7 mg/10 mg, taken once daily in the evening. The dose should be increased in 7 mg increments to the recommended maintenance dose of 28 mg/10 mg. The minimum recommended interval between dose increases is one week. (2.1)
- Patients on memantine hydrochloride (10 mg twice daily or 28 mg extended-release once daily) and donepezil hydrochloride 10 mg once daily can be switched to NAMZARIC 28 mg/10 mg, taken once daily in the evening. (2.1)
- NAMZARIC can be taken with or without food, whole or sprinkled on applesauce; do not divide, chew, or crush. (2.2)
- Severe renal impairment: the recommended maintenance dose for NAMZARIC is 14 mg/10 mg once daily in the evening. (2.3)

---------- DOSAGE FORMS AND STRENGTHS----------

-Extended-Release Capsules:

- 7 mg memantine hydrochloride and 10 mg donepezil hydrochloride (3)
- 14 mg memantine hydrochloride and 10 mg donepezil hydrochloride (3)
- 21 mg memantine hydrochloride and 10 mg donepezil hydrochloride (3)
- 28 mg memantine hydrochloride and 10 mg donepezil hydrochloride (3)

---------- CONTRAINDICATIONS ----------

NAMZARIC is contraindicated in patients with known hypersensitivity to memantine hydrochloride, donepezil hydrochloride, piperidine derivatives, or to any excipients used in the formulation. (4)

---------- WARNINGS AND PRECAUTIONS--- ----------

- NAMZARIC is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia. (5.1)
- NAMZARIC may have vagotonic effects on the sinoatrial and atrioventricular nodes manifesting as bradycardia or heart block. (5.2)
- Monitor patients for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers. (5.3)
- NAMZARIC can cause diarrhea, nausea, and vomiting. (5.4)
- NAMZARIC may cause bladder outflow obstructions. (5.5)
- Conditions that raise urine pH may decrease the urinary elimination of memantine, resulting in increased plasma levels of memantine. (5.5, 7.1)

---------- ADVERSE REACTIONS----------

- The most common adverse reactions, occurring at a frequency of at least 5% and greater than placebo with memantine hydrochloride extended-release 28 mg/day, were headache, diarrhea, and dizziness. (6.1)
- The most common adverse reactions, occurring at a frequency of at least 5% in patients receiving donepezil hydrochloride and at twice or more the placebo rate, include diarrhea, anorexia, vomiting, nausea, and ecchymosis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Forest Laboratories, LLC. at 1-800-678-1605 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------

- Combined use with NMDA antagonists: use with caution. (7.2)
- NAMZARIC may interfere with anticholinergic medications. (7.4)
- Concomitant administration of succinylcholine, similar neuromuscular blocking agents, or cholinergic agonists may lead to synergistic effect. (7.5)

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

Revised: 07/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NAMZARIC is indicated for the treatment of moderate to severe dementia of the Alzheimer's type in patients stabilized on 10 mg of donepezil hydrochloride once daily.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose of NAMZARIC is 28 mg/10 mg once daily.

For patients stabilized on donepezil and not currently on memantine:
For patients stabilized on donepezil hydrochloride 10 mg and not currently on memantine hydrochloride, the recommended starting dose of NAMZARIC is 7 mg/10 mg, taken once a day in the evening. The dose should be increased in 7 mg increments of the memantine hydrochloride component to the recommended maintenance dose of 28 mg/10 mg once daily. The minimum recommended interval between dose increases is one week. The dose should only be increased if the previous dose has been well tolerated. The maximum dose is 28 mg/10 mg once daily.

For patients stabilized on both donepezil and memantine:
Patients stabilized on memantine hydrochloride (10 mg twice daily or 28 mg extended-release once daily) and donepezil hydrochloride 10 mg once daily can be switched to NAMZARIC 28 mg/10 mg, taken once a day in the evening. Patients should start NAMZARIC the day following the last dose of memantine hydrochloride and donepezil hydrochloride administered separately.

If a patient misses a single dose of NAMZARIC, the next dose should be taken as scheduled, without doubling up the dose.

2.2 Administration Information

NAMZARIC can be taken with or without food. NAMZARIC capsules can be taken intact or may be opened, sprinkled on applesauce, and swallowed without chewing. The entire contents of each NAMZARIC capsule should be consumed; the dose should not be divided.

Except when opened and sprinkled on applesauce, as described above, NAMZARIC capsules should be swallowed whole. NAMZARIC capsules should not be divided, chewed, or crushed.

2.3 Dosing in Patients with Severe Renal Impairment

For patients stabilized on donepezil and not currently on memantine:
For patients with severe renal impairment (creatinine clearance 5-29 mL/min, based on the Cockcroft-Gault equation) stabilized on donepezil hydrochloride 10 mg once daily and not currently on memantine hydrochloride, the recommended starting dose of NAMZARIC is 7

mg/10 mg taken once a day in the evening. The dose should be increased to the recommended maintenance dose of 14 mg/10 mg once daily in the evening after a minimum of one week *[see Use in Specific Populations (8.6)]*.

For patients stabilized on both donepezil and memantine:
Patients with severe renal impairment, stabilized on memantine hydrochloride (5 mg twice daily or 14 mg extended-release once daily) and donepezil hydrochloride 10 mg once daily, can be switched to NAMZARIC 14 mg/10 mg, taken once daily in the evening.

3 DOSAGE FORMS AND STRENGTHS

Extended-Release Capsules:

- 7 mg memantine hydrochloride and 10 mg donepezil hydrochloride: light green opaque body and an orange opaque cap with a black “FL 7/10” radial imprint
- 14 mg memantine hydrochloride and 10 mg donepezil hydrochloride: light green opaque capsules with a black “FL 14/10” radial imprint
- 21 mg memantine hydrochloride and 10 mg donepezil hydrochloride: white opaque body and an orange opaque cap with a black “FL 21/10” radial imprint
- 28 mg memantine hydrochloride and 10 mg donepezil hydrochloride: blue opaque capsules with a black “FL 28/10” radial imprint

4 CONTRAINDICATIONS

NAMZARIC is contraindicated in patients with known hypersensitivity to memantine hydrochloride, donepezil hydrochloride, piperidine derivatives, or to any excipients used in the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Anesthesia

Donepezil hydrochloride, an active ingredient in NAMZARIC, 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, an active ingredient in NAMZARIC.

5.3 Peptic Ulcer Disease and Gastrointestinal Bleeding

Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. 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. Patients treated with NAMZARIC 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).

5.4 Nausea and Vomiting

Donepezil hydrochloride, an active ingredient in NAMZARIC, when initiated, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea, and vomiting. Although in most cases, these effects have been mild and 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.

5.5 Genitourinary Conditions

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

Conditions that raise urine pH may decrease the urinary elimination of memantine, an active ingredient in NAMZARIC, resulting in increased plasma levels of memantine *[see Drug Interactions (7.1)]*.

5.6 Seizures

Cholinomimetics, including donepezil hydrochloride, an active ingredient in NAMZARIC, are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a manifestation of Alzheimer's disease.

5.7 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 discussed below and elsewhere in the labeling.

- Cardiovascular Conditions *[see Warnings and Precautions (5.2)]*
- Peptic Ulcer Disease and Gastrointestinal Bleeding *[see Warnings and Precautions (5.3)]*
- Nausea and Vomiting *[see Warnings and Precautions (5.4)]*
- Genitourinary Conditions *[see Warnings and Precautions (5.5)]*
- Seizures *[see Warnings and Precautions (5.6)]*

- Pulmonary Conditions *[see Warnings and Precautions (5.7)]*

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.

Memantine Hydrochloride

Memantine hydrochloride extended-release was evaluated in a double-blind, placebo-controlled trial in 676 patients with moderate to severe dementia of the Alzheimer's type (341 patients treated with memantine 28 mg/day dose and 335 patients treated with placebo) for a treatment period up to 24 weeks. Of the patients randomized, 236 treated with memantine 28 mg/day and 227 treated with placebo were on a stable dose of donepezil for 3 months prior to screening.

Adverse Reactions Leading to Discontinuation with Memantine Hydrochloride

In the placebo-controlled clinical trial of memantine hydrochloride extended-release, the proportion of patients in the memantine hydrochloride extended-release 28 mg/day dose group and in the placebo group who discontinued treatment due to adverse reactions was 10% and 6%, respectively. The most common adverse reaction in the memantine hydrochloride extended-release treated group that led to treatment discontinuation was dizziness, at a rate of 1.5%.

Most Common Adverse Reactions with Memantine Hydrochloride

The most common adverse reactions with memantine hydrochloride extended-release in patients with moderate to severe Alzheimer's disease, defined as those occurring at a frequency of at least 5% in the memantine hydrochloride extended-release group and at a higher frequency than placebo, were headache, diarrhea, and dizziness.

Table 1 lists adverse reactions that occurred at an incidence of ≥ 2% in the memantine hydrochloride extended-release treated group and occurred at a rate greater than placebo.

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