

NDA 22525

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NAMENDA XR capsules safely and effectively. See full prescribing information for NAMENDA XR capsules.

NAMENDA XR (memantine hydrochloride) extended release capsules
Initial U.S. Approval: 2003

INDICATIONS AND USAGE

NAMENDA XR contains memantine HCl, an NMDA receptor antagonist indicated for the treatment of moderate to severe dementia of the Alzheimer's type. (1)

DOSAGE AND ADMINISTRATION

Initial Dose 7 mg NAMENDA XR once daily (2.1)
Maintenance Dose 28 mg NAMENDA XR once daily (2.1)

A minimum of 1 week of treatment with the previous dose should be observed before increasing the dose. (2.1)

A target dose of 14 mg once daily is recommended in patients with severe renal impairment. (2.1)

DOSAGE FORMS AND STRENGTHS

NAMENDA XR is available as an extended-release capsule (3.1) in the following strengths: 7 mg, 14 mg, 21 mg, 28 mg (3.1, 3.2)

CONTRAINDICATIONS

NAMENDA XR is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation. (4.1)

WARNINGS AND PRECAUTIONS

Conditions that raise urine pH may decrease the urinary elimination of memantine resulting in increased plasma levels of memantine. (5.1)

ADVERSE REACTIONS

The most commonly observed adverse reactions occurring at a frequency of at least 5% and greater than placebo with administration of NAMENDA XR 28 mg/day were headache, diarrhea and dizziness. Other less common and sometimes serious adverse events have been reported. (6)

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

DRUG INTERACTIONS

Use with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) has not been systematically evaluated and such use should be approached with caution. (7.1)

USE IN SPECIFIC POPULATIONS

Pediatric Use: The safety and effectiveness of NAMENDA XR in pediatric patients have not been established. (8.3)

PATIENT COUNSELING INFORMATION

See Section 17 for PATIENT COUNSELING INFORMATION AND FDA approved patient labeling.

REVISED: [06/2010]

FULL PRESCRIBING INFORMATION: CONTENTS*

| | |
|---|---|
| 1. INDICATIONS AND USAGE | 7.4 Drugs Eliminated via Renal Mechanisms |
| 2. DOSAGE AND ADMINISTRATION | 7.5 Drugs that Make the Urine Alkaline |
| 2.1 Recommended Dosing | 7.6 Drugs Highly Bound to Plasma Proteins |
| 3. DOSAGE FORMS AND STRENGTHS | 7.7 Use with Cholinesterase Inhibitors |
| 3.1 Dosage Form | 8. USE IN SPECIFIC POPULATIONS |
| 3.2 Dosage Strengths | 8.1 Pregnancy |
| 4. CONTRAINDICATIONS | 8.3 Nursing Mothers |
| 4.1 Hypersensitivity | 8.4 Pediatric Use |
| 5. WARNINGS AND PRECAUTIONS | 9. DRUG DEPENDENCE |
| 5.1 Genitourinary Conditions | 10. OVERDOSAGE |
| 5.2 Seizures | 11. DESCRIPTION |
| 6. ADVERSE REACTIONS | 12. CLINICAL PHARMACOLOGY |
| 6.1 Clinical Trial Data Sources | 12.1 Mechanism of Action |
| 6.2 Adverse Reactions Leading to Discontinuation | 12.2 Pharmacodynamics |
| 6.3 Most Common Adverse Reactions | 12.3 Pharmacokinetics |
| 6.4 Vital Sign Changes | 12.4 Pharmacokinetics in Special Populations |
| 6.5 Laboratory Changes | 13. NONCLINICAL TOXICOLOGY |
| 6.6 ECG Changes | 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility |
| 6.7 Other Adverse Reactions Observed During Clinical Trials of Namenda XR | 13.2 Animal Toxicology |
| 6.8 Memantine Immediate Release Clinical Trial and Post Marketing Spontaneous Reports | 14. CLINICAL STUDIES |
| 7. DRUG INTERACTIONS | 16. HOW SUPPLIED/ STORAGE AND HANDLING |
| 7.1 Use with Other N-methyl-D-aspartate Antagonists | 17. PATIENT COUNSELING INFORMATION |
| 7.2 Effect of Memantine on the Metabolism of Other Drugs | |
| 7.3 Effect of Other Drugs on Memantine | |

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

NDA 22525

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NAMENDA XR (memantine hydrochloride) extended-release capsules are indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The dosage of NAMENDA XR shown to be effective in a controlled clinical trial is 28 mg once daily.

The recommended starting dose of NAMENDA XR is 7 mg once daily. The recommended target dose is 28 mg once daily. The dose should be increased in 7 mg increments to 28 mg once daily. The minimum recommended interval between dose increases is one week, and only if the previous dose has been well tolerated. The maximum recommended dose is 28 mg once daily.

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

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

Switching from NAMENDA Tablets to NAMENDA XR Capsules:

Patients treated with NAMENDA tablets may be switched to NAMENDA XR capsules as follows:

It is recommended that a patient who is on a regimen of 10 mg twice daily of NAMENDA tablets be switched to NAMENDA XR 28 mg once daily capsules the day following the last dose of a 10 mg NAMENDA tablet. There is no study addressing the comparative efficacy of these 2 regimens.

In a patient with severe renal impairment, it is recommended that a patient who is on a regimen of 5 mg twice daily of NAMENDA tablets be switched to NAMENDA XR 14 mg once daily capsules the day following the last dose of a 5 mg NAMENDA tablet.

Special Populations:

Hepatic Impairment

No dosage adjustment is recommended in patients with mild or moderate hepatic impairment. NAMENDA XR should be administered with caution to patients with severe hepatic impairment.

Renal Impairment

No dosage adjustment is recommended in patients with mild or moderate renal impairment.

A target dose of 14 mg/day is recommended in patients with severe renal impairment (creatinine clearance of 5 – 29 mL/min, based on the Cockcroft-Gault equation).

NDA 22525

3 DOSAGE FORMS AND STRENGTHS

3.1 Dosage Form

Capsule:

Each capsule contains 7 mg, 14 mg, 21 mg or 28 mg of memantine HCl.

The 7 mg capsules are a yellow opaque #4 size capsule, with “FLI 7 mg” black imprint.

The 14 mg capsules are a yellow cap and dark green opaque body #4 size capsule, with “FLI 14 mg” black imprint on the yellow cap.

The 21 mg capsules are a white to off-white cap and dark green opaque body #4 size capsule, with “FLI 21 mg” black imprint on the white to off-white cap.

The 28 mg capsules are a dark green opaque #3 size capsule, with “FLI 28 mg” white imprint.

3.2 Dosage Strengths

- Each 7 mg capsule contains 7 mg memantine HCl.
- Each 14 mg capsule contains 14 mg memantine HCl.
- Each 21 mg capsule contains 21 mg memantine HCl.
- Each 28 mg capsule contains 28 mg memantine HCl.

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

4 CONTRAINDICATIONS

4.1 Hypersensitivity

NAMENDA XR is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation [*see Description (11)*].

5 WARNINGS AND PRECAUTIONS

5.1 Genitourinary Conditions

Conditions that raise urine pH may decrease the urinary elimination of memantine resulting in increased plasma levels of memantine.

5.2 Seizures

NAMENDA XR has not been systematically evaluated in patients with a seizure disorder. In clinical trials of memantine, seizures occurred in 0.3% of patients treated with memantine and 0.6% of patients treated with placebo.

NDA 22525

6 ADVERSE REACTIONS

6.1 Clinical Trial Data Sources

NAMENDA XR was evaluated in a double-blind placebo-controlled trial treating a total of 676 patients with moderate to severe dementia of the Alzheimer's type (341 patients treated with NAMENDA XR 28 mg/day dose and 335 patients treated with placebo) for a treatment period up to 24 weeks.

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.

6.2 Adverse Reactions Leading to Discontinuation

In the placebo-controlled clinical trial of NAMENDA XR (see *Clinical Studies (14)*), which treated a total of 676 patients, the proportion of patients in the NAMENDA XR 28 mg/day dose and placebo groups who discontinued treatment due to adverse events were 10.0% and 6.3%, respectively. The most common adverse reaction in the NAMENDA XR treated group that led to treatment discontinuation in this study was dizziness at a rate of 1.5%.

6.3 Most Common Adverse Reactions

The most commonly observed adverse reactions seen in patients administered NAMENDA XR in the controlled clinical trial, defined as those occurring at a frequency of at least 5% in the NAMENDA XR group and at a higher frequency than placebo were headache, diarrhea and dizziness.

Table 1 lists treatment-emergent adverse reactions that were observed at an incidence of $\geq 2\%$ in the NAMENDA XR treated group and occurred at a rate greater than placebo.

Table 1: Adverse reactions observed with a frequency of $\geq 2\%$ and occurring with a rate greater than placebo

| Adverse reaction | Placebo (n = 335) % | NAMENDA XR 28mg (n = 341) % |
|---|------------------------------------|--|
| Gastrointestinal Disorders | | |
| Diarrhea | 4 | 5 |
| Constipation | 1 | 3 |
| Abdominal pain | 1 | 2 |
| Vomiting | 1 | 2 |
| Infections and infestations | | |
| Influenza | 3 | 4 |
| Investigations | | |
| Weight, increased | 1 | 3 |
| Musculoskeletal and connective tissue disorders | | |
| Back pain | 1 | 3 |
| Nervous system disorders | | |

NDA 22525

Table 1: Adverse reactions observed with a frequency of $\geq 2\%$ and occurring with a rate greater than placebo

| <i>Adverse reaction</i> | <i>Placebo (n = 335) %</i> | <i>NAMENDA XR 28mg (n = 341) %</i> |
|-----------------------------|------------------------------------|--|
| Headache | 5 | 6 |
| Dizziness | 1 | 5 |
| Somnolence | 1 | 3 |
| Psychiatric disorders | | |
| Anxiety | 3 | 4 |
| Depression | 1 | 3 |
| Aggression | 1 | 2 |
| Renal and urinary disorders | | |
| Urinary incontinence | 1 | 2 |
| Vascular disorders | | |
| Hypertension | 2 | 4 |
| Hypotension | 1 | 2 |

6.4 Vital Sign Changes

NAMENDA XR and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, diastolic blood pressure, and weight) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. There were no clinically important changes in vital signs in patients treated with NAMENDA XR. A comparison of supine and standing vital sign measures for NAMENDA XR and placebo in Alzheimer's patients indicated that NAMENDA XR treatment is not associated with orthostatic changes.

6.5 Laboratory Changes

NAMENDA XR and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with NAMENDA XR treatment.

6.6 ECG Changes

NAMENDA XR and placebo groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in ECG parameters associated with NAMENDA XR treatment.

NDA 22525

6.7 Other Adverse Reactions Observed During Clinical Trials of NAMENDA XR

Following is a list of treatment-emergent adverse reactions reported from 750 patients treated with NAMENDA XR for periods up to 52 weeks in double-blind or open-label clinical trials. The listing does not include those events already listed in Table 1, those events for which a drug cause was remote, those events for which descriptive terms were so lacking in specificity as to be uninformative, and those events reported only once which did not have a substantial probability of being immediately life threatening. Events are categorized by body system.

Blood and Lymphatic System Disorders: anemia.

Cardiac Disorders: bradycardia, myocardial infarction.

Gastrointestinal Disorders: fecal incontinence, nausea.

General Disorders: asthenia, fatigue, gait disturbance, irritability, peripheral edema, pyrexia.

Infections and Infestations: bronchitis, nasopharyngitis, pneumonia, upper respiratory tract infection, urinary tract infection.

Injury, Poisoning and Procedural Complications: fall.

Investigations: weight decreased.

Metabolism and Nutrition Disorders: anorexia, dehydration, decreased appetite, hyperglycemia.

Musculoskeletal and Connective Tissue Disorders: arthralgia, pain in extremity.

Nervous System Disorders: convulsion, dementia Alzheimer's type, syncope, tremor.

Psychiatric Disorders: agitation, confusional state, delirium, delusion, disorientation, hallucination, insomnia, restlessness.

Respiratory, Thoracic and Mediastinal Disorders: cough, dyspnea.

6.8 Memantine Immediate Release Clinical Trial and Post Marketing Spontaneous Reports

The following additional adverse reactions have been identified from previous worldwide experience with memantine (immediate release) use. These adverse reactions have been chosen for inclusion because of a combination of seriousness, frequency of reporting, or potential causal connection to memantine and have not been listed elsewhere in labeling. However, because some of these adverse reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship between their occurrence and the administration of memantine. These events include:

Blood and Lymphatic System Disorders: agranulocytosis, leukopenia (including neutropenia), pancytopenia, thrombocytopenia, thrombotic thrombocytopenic purpura.

Cardiac Disorders: atrial fibrillation, atrioventricular block (including 2nd and 3rd degree block), cardiac failure, orthostatic hypotension, and torsades de pointes.

Endocrine Disorders: inappropriate antidiuretic hormone secretion.

Gastrointestinal disorders: colitis, pancreatitis.

General disorders and administration site conditions: malaise, sudden death.

NDA 22525

Hepatobiliary Disorders: hepatitis (including abnormal hepatic function test, cytolytic and cholestatic hepatitis), hepatic failure.

Infections and infestations: sepsis.

Investigations: electrocardiogram QT prolonged, international normalized ratio increased.

Metabolism and Nutrition Disorders: hypoglycaemia, hyponatraemia.

Nervous System Disorders: convulsions (including grand mal), cerebrovascular accident, dyskinesia, extrapyramidal disorder, hypertonia, loss of consciousness, neuroleptic malignant syndrome, Parkinsonism, tardive dyskinesia, transient ischemic attack.

Psychiatric Disorders: hallucinations (both visual and auditory), restlessness, suicidal ideation.

Renal and Urinary Disorders: acute renal failure (including abnormal renal function test), urinary retention.

Skin Disorders: rash, Stevens Johnson syndrome.

Vascular Disorders: pulmonary embolism, thrombophlebitis, deep venous thrombosis.

The following adverse events have been reported to be temporally associated with memantine treatment and are not described elsewhere in the product labeling: aspiration pneumonia, bone fracture, carpal tunnel syndrome, cerebral infarction, chest pain, cholelithiasis, claudication, depressed level of consciousness (including rare reports of coma), dysphagia, encephalopathy, gastritis, gastroesophageal reflux, intracranial hemorrhage, hyperglycemia, hyperlipidemia, ileus, impotence, lethargy, myoclonus, supraventricular tachycardia, and tachycardia. However, there is again no evidence that any of these additional adverse events are caused by memantine.

7 DRUG INTERACTIONS

No drug-drug interaction studies have been conducted with NAMENDA XR, specifically,

7.1 Use with other N-methyl-D-aspartate (NMDA) Antagonists

The combined use of NAMENDA XR with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) has not been systematically evaluated and such use should be approached with caution.

7.2 Effect of Memantine on the Metabolism of Other Drugs

In vitro studies conducted with marker substrates of CYP450 enzymes (CYP1A2, -2A6, -2C9, -2D6, -2E1, -3A4) showed minimal inhibition of these enzymes by memantine. In addition, *in vitro* studies indicate that at concentrations exceeding those associated with efficacy, memantine does not induce the cytochrome P450 isozymes CYP1A2, -2C9, -2E1 and -3A4/5. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected.

Pharmacokinetic studies evaluated the potential of memantine for interaction with donepezil (See *Section 7.7 Use with Cholinesterase Inhibitors*) and bupropion. Coadministration of memantine with the AChE inhibitor donepezil HCl does not affect the pharmacokinetics of either compound. Memantine did not affect the pharmacokinetics of the CYP2B6 substrate bupropion or its metabolite hydroxybupropion.

NDA 22525

7.3 Effect of Other Drugs on Memantine

Memantine is predominantly renally eliminated, and drugs that are substrates and/or inhibitors of the CYP450 system are not expected to alter the pharmacokinetics of memantine. A clinical drug-drug interaction study indicated that bupropion did not affect the pharmacokinetics of memantine.

7.4 Drugs Eliminated via Renal Mechanisms

Because memantine is eliminated in part by tubular secretion, coadministration of drugs that use the same renal cationic system, including hydrochlorothiazide (HCTZ), triamterene (TA), metformin, cimetidine, ranitidine, quinidine, and nicotine, could potentially result in altered plasma levels of both agents. However, coadministration of memantine and HCTZ/TA did not affect the bioavailability of either memantine or TA, and the bioavailability of HCTZ decreased by 20%. In addition, coadministration of memantine with the antihyperglycemic drug Glucovance[®] (glyburide and metformin HCl) did not affect the pharmacokinetics of memantine, metformin and glyburide. Furthermore, memantine did not modify the serum glucose lowering effect of Glucovance[®], indicating the absence of a pharmacodynamic interaction.

7.5 Drugs That Make the Urine Alkaline

The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by diet, drugs (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) and clinical state of the patient (e.g. renal tubular acidosis or severe infections of the urinary tract). Hence, memantine should be used with caution under these conditions.

7.6 Drugs Highly Bound to Plasma Proteins

Because the plasma protein binding of memantine is low (45%), an interaction with drugs that are highly bound to plasma proteins, such as warfarin and digoxin, is unlikely [see Section 7.].

7.7 Use with Cholinesterase Inhibitors

Coadministration of memantine with the AChE inhibitor donepezil HCl did not affect the pharmacokinetics of either compound. In a 24-week controlled clinical study in patients with moderate to severe Alzheimer's disease, the adverse event profile observed with a combination of memantine immediate-release and donepezil was similar to that of donepezil alone.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B: There are no adequate and well-controlled studies of NAMENDA XR in pregnant women. NAMENDA XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Memantine given orally to pregnant rats and pregnant rabbits during the period of organogenesis was not teratogenic up to the highest doses tested (18 mg/kg/day in rats and 30 mg/kg/day in rabbits, which are 6 and 21 times, respectively, the maximum recommended human dose [MRHD] on a mg/m² basis).

NDA 22525

Slight maternal toxicity, decreased pup weights and an increased incidence of non-ossified cervical vertebrae were seen at an oral dose of 18 mg/kg/day in a study in which rats were given oral memantine beginning pre-mating and continuing through the postpartum period. Slight maternal toxicity and decreased pup weights were also seen at this dose in a study in which rats were treated from day 15 of gestation through the post-partum period. The no-effect dose for these effects was 6 mg/kg, which is 2 times the MRHD on a mg/m² basis.

8.3 Nursing Mothers

It is not known whether memantine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when memantine is administered to a nursing mother.

8.4 Pediatric Use

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

9 DRUG ABUSE AND DEPENDENCE

Memantine is not a controlled substance. Memantine is a low to moderate affinity uncompetitive NMDA antagonist that did not produce any evidence of drug-seeking behavior or withdrawal symptoms upon discontinuation in 3,254 patients who participated in clinical trials at therapeutic doses. Post marketing data, outside the U.S., retrospectively collected, has provided no evidence of drug abuse or dependence.

10 OVERDOSAGE

Signs and symptoms most often accompanying overdose with other formulations of memantine in clinical trials and from worldwide marketing experience, alone or in combination with other drugs and/or alcohol, include agitation, asthenia, bradycardia, confusion, coma, dizziness, ECG changes, increased blood pressure, lethargy, loss of consciousness, psychosis, restlessness, slowed movement, somnolence, stupor, unsteady gait, visual hallucinations, vertigo, vomiting, and weakness. The largest known ingestion of memantine worldwide was 2 grams in an individual who took memantine in conjunction with unspecified antidiabetic medications. This person experienced coma, diplopia, and agitation, but subsequently recovered.

One patient participating in a NAMENDA XR clinical trial unintentionally took 112 mg of NAMENDA XR daily for 31 days and experienced an elevated serum uric acid, elevated serum alkaline phosphatase, and low platelet count.

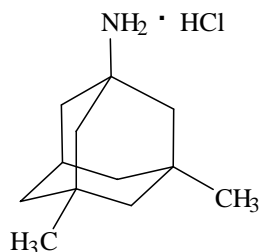
No fatalities have been noted with overdoses of memantine alone. A fatal outcome has very rarely been reported when memantine has been ingested as part of overdosing with multiple drugs; in those instances, the relationship between memantine and a fatal outcome has been unclear.

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 cases of overdose, general supportive measures should be utilized, and treatment should be symptomatic. Elimination of memantine can be enhanced by acidification of urine.

11 DESCRIPTION

NAMENDA XR is an orally active NMDA receptor antagonist. The chemical name for memantine hydrochloride is 1-amino-3,5-dimethyladamantane hydrochloride with the following structural formula:

NDA 22525



The molecular formula is C₁₂H₂₁N•HCl and the molecular weight is 215.76. Memantine HCl occurs as a fine white to off-white powder and is soluble in water.

NAMENDA XR capsules are supplied for oral administration as 7, 14, 21 and 28 mg capsules (see *How Supplied* Section 16). Each capsule contains extended release beads with the labeled amount of memantine HCl and the following inactive ingredients: sugar spheres, polyvinylpyrrolidone, hypromellose, talc, polyethylene glycol, ethylcellulose, ammonium hydroxide, oleic acid, and medium chain triglycerides in hard gelatin capsules.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Persistent activation of central nervous system N-methyl-D-aspartate (NMDA) receptors by the excitatory amino acid glutamate has been hypothesized to contribute to the symptomatology of Alzheimer's disease. Memantine is postulated to exert its therapeutic effect through its action as a low to moderate affinity uncompetitive (open-channel) NMDA receptor antagonist which binds preferentially to the NMDA receptor-operated cation channels. There is no evidence that memantine prevents or slows neurodegeneration in patients with Alzheimer's disease.

12.2 Pharmacodynamics

Memantine showed low to negligible affinity for GABA, benzodiazepine, dopamine, adrenergic, histamine and glycine receptors and for voltage-dependent Ca²⁺, Na⁺ or K⁺ channels. Memantine also showed antagonistic effects at the 5HT₃ receptor with a potency similar to that for the NMDA receptor and blocked nicotinic acetylcholine receptors with one-sixth to one-tenth the potency.

In vitro studies have shown that memantine does not affect the reversible inhibition of acetylcholinesterase by donepezil, galantamine, or tacrine.

12.3 Pharmacokinetics

Memantine is well absorbed after oral administration and has linear pharmacokinetics over the therapeutic dose range. It is excreted predominantly unchanged in urine and has a terminal elimination half life of about 60-80 hours. In a study comparing 28 mg once daily NAMENDA XR to 10 mg twice daily NAMENDA C_{max} and AUC₀₋₂₄ values were 48% and 33% higher for the XR dosage regimen, respectively.

Absorption

After multiple dose administration of NAMENDA XR, memantine peak concentrations occur around 9-12 hours postdose. There is no difference in the absorption of NAMENDA XR when the capsule is taken intact or when the contents are sprinkled on applesauce.

There is no difference in memantine exposure, based on C_{max} or AUC, for NAMENDA XR whether that drug product is administered with food or on an empty stomach. However, peak

NDA 22525

plasma concentrations are achieved about 18 hours after administration with food versus approximately 25 hours after administration on an empty stomach.

Distribution

The mean volume of distribution of memantine is 9-11 L/kg and the plasma protein binding is low (45%).

Metabolism

Memantine undergoes partial hepatic metabolism. The hepatic microsomal CYP450 enzyme system does not play a significant role in the metabolism of memantine.

Elimination

Memantine is excreted predominantly in the urine, unchanged, and has a terminal elimination half life of about 60-80 hours. About 48% of administered drug is excreted unchanged in urine; the remainder is converted primarily to three polar metabolites which possess minimal NMDA receptor antagonistic activity: the N-glucuronide conjugate, 6-hydroxy memantine, and 1-nitroso-deaminated memantine. A total of 74% of the administered dose is excreted as the sum of the parent drug and the N-glucuronide conjugate. Renal clearance involves active tubular secretion moderated by pH dependent tubular reabsorption.

12.4 Pharmacokinetics in Special Populations

Hepatic Impairment

Memantine pharmacokinetics were evaluated following the administration of single oral doses of 20 mg in 8 subjects with moderate hepatic impairment (Child-Pugh Class B, score 7-9) and 8 subjects who were age-, gender-, and weight-matched to the hepatically-impaired subjects. There was no change in memantine exposure (based on C_{max} and AUC) in subjects with moderate hepatic impairment as compared with healthy subjects. However, terminal elimination half-life increased by about 16% in subjects with moderate hepatic impairment as compared with healthy subjects. No dose adjustment is recommended for patients with mild and moderate hepatic impairment. NAMENDA XR should be administered with caution to patients with severe hepatic impairment as the pharmacokinetics of memantine have not been evaluated in that population.

Renal Impairment

Memantine pharmacokinetics were evaluated following single oral administration of 20 mg memantine HCl in 8 subjects with mild renal impairment (creatinine clearance, CL_{cr}, > 50 – 80 mL/min), 8 subjects with moderate renal impairment (CL_{cr} 30 – 49 mL/min), 7 subjects with severe renal impairment (CL_{cr} 5 – 29 mL/min) and 8 healthy subjects (CL_{cr} > 80 mL/min) matched as closely as possible by age, weight and gender to the subjects with renal impairment. Mean AUC_{0-∞} increased by 4%, 60%, and 115% in subjects with mild, moderate, and severe renal impairment, respectively, compared to healthy subjects. The terminal elimination half-life increased by 18%, 41%, and 95% in subjects with mild, moderate, and severe renal impairment, respectively, compared to healthy subjects.

No dosage adjustment is recommended for patients with mild and moderate renal impairment. Dosage should be reduced in patients with severe renal impairment [See *Dosage and Administration (2)*].

NDA 22525

Gender

Following multiple dose administration of memantine HCl 20 mg daily, females had about 45% higher exposure than males, but there was no difference in exposure when body weight was taken into account.

Elderly

The pharmacokinetics of memantine in young and elderly subjects are similar.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of carcinogenicity in a 113-week oral study in mice at doses up to 40 mg/kg/day (7 times the maximum recommended human dose [MRHD] on a mg/m² basis). There was also no evidence of carcinogenicity in rats orally dosed at up to 40 mg/kg/day for 71 weeks followed by 20 mg/kg/day (14 and 7 times the MRHD on a mg/m² basis, respectively) through 128 weeks.

Memantine produced no evidence of genotoxic potential when evaluated in the *in vitro* *S. typhimurium* or *E. coli* reverse mutation assay, an *in vitro* chromosomal aberration test in human lymphocytes, an *in vivo* cytogenetics assay for chromosome damage in rats, and the *in vivo* mouse micronucleus assay. The results were equivocal in an *in vitro* gene mutation assay using Chinese hamster V79 cells.

No impairment of fertility or reproductive performance was seen in rats administered up to 18 mg/kg/day (6 times the MRHD on a mg/m² basis) orally from 14 days prior to mating through gestation and lactation in females, or for 60 days prior to mating in males.

13.2 Animal Toxicology

Memantine induced neuronal lesions (vacuolation and necrosis) in the multipolar and pyramidal cells in cortical layers III and IV of the posterior cingulate and retrosplenial neocortices in rats, similar to those which are known to occur in rodents administered other NMDA receptor antagonists. Lesions were seen after a single dose of memantine. In a study in which rats were given daily oral doses of memantine for 14 days, the no-effect dose for neuronal necrosis was 4 times the maximum recommended human dose (MRHD of 28 mg/day) on a mg/m² basis.

In a neurotoxicity study, female rats were given oral doses of memantine (3, 10, 30, 60 mg/kg/day) alone or in combination with donepezil (3, 10 mg/kg/day) for 28 days. When administered alone, memantine induced neurodegeneration only at 60 mg/kg/day; however, when administered in combination with 10 mg/kg/day donepezil, memantine induced neurodegeneration at doses of 30 and 60 mg/kg/day. When 60 mg/kg/day memantine and 10 mg/kg/day donepezil were administered in combination, the incidence and severity of neurodegeneration was increased compared to that with 60 mg/kg/day memantine alone or with 30 mg/kg/day memantine in combination with 10 mg/kg/day donepezil. In addition, the combination of 60 mg/kg/day memantine and 10 mg/kg/day donepezil was associated with widespread neurodegeneration in cortical areas (perirhinal, temporal, entorhinal, frontal, insular, piriform) and in olfactory nucleus and subiculum, whereas in the other affected groups, there was limited cortical (entorhinal, retrosplenial) involvement. At the no-effect level of the combination (10 mg/kg/day memantine + 10 mg/kg/day donepezil), plasma exposures of memantine were similar to (AUC) or two times (C_{max}) those expected in humans at the MRHD; plasma exposures of donepezil were 3 (AUC) or 6 (C_{max}) times those in humans at the MRHD of donepezil (10 mg/day). In a published study, similar donepezil-mediated exacerbation of memantine-induced neurodegeneration was observed in female rats given single doses of memantine in combination with donepezil, both administered by intraperitoneal injection.

NDA 22525

The potential for induction of central neurodegenerative lesions by NMDA receptor antagonists in humans is unknown.

14 CLINICAL STUDIES

The effectiveness of NAMENDA XR as a treatment for patients with moderate to severe Alzheimer's disease was based on the results of a double-blind, placebo-controlled trial.

14.1 24-week Study of NAMENDA XR Capsules

This was a randomized double-blind clinical investigation in outpatients with moderate to severe Alzheimer's disease (diagnosed by DSM-IV criteria and NINCDS-ADRDA criteria for AD with a Mini Mental State Examination (MMSE) score ≥ 3 and ≤ 14 at Screening and Baseline) receiving acetylcholinesterase inhibitor (AChEI) therapy at a stable dose for 3 months prior to screening. The mean age of patients participating in this trial was 76.5 years with a range of 49-97 years. Approximately 72% of patients were female and 94% were Caucasian.

14.2 Study Outcome Measures

The effectiveness of NAMENDA XR was evaluated in this study using the co-primary efficacy parameters of Severe Impairment Battery (SIB) and the Clinician's Interview-Based Impression of Change (CIBIC-Plus).

The ability of NAMENDA XR to improve cognitive performance was assessed with the Severe Impairment Battery (SIB), a multi-item instrument that has been validated for the evaluation of cognitive function in patients with moderate to severe dementia. The SIB examines selected aspects of cognitive performance, including elements of attention, orientation, language, memory, visuospatial ability, construction, praxis, and social interaction. The SIB scoring range is from 0 to 100, with lower scores indicating greater cognitive impairment.

The ability of NAMENDA XR 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 ADCS-ADL or SIB. 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 this trial was a structured instrument based on a comprehensive evaluation at baseline and subsequent time-points of four domains: general (overall clinical status), functional (including activities of daily living), cognitive, and behavioral. It represents the assessment of a skilled clinician using validated scales based on his/her observation during 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 "marked improvement" to a score of 4, indicating "no change" to a score of 7, indicating "marked worsening." The CIBIC-Plus has not been systematically compared directly to assessments not using information from caregivers (CIBIC) or other global methods.

14.3 Study Results

In this study, 677 patients were randomized to one of the following 2 treatments: NAMENDA XR 28 mg/day or placebo while still receiving an AChEI (either donepezil, galantamine, or rivastigmine).

NDA 22525

Effects on Severe Impairment Battery (SIB)

Figure 1 shows the time course for the change from baseline in SIB score for the two treatment groups completing the 24 weeks of the study. At 24 weeks of treatment, the mean difference in the SIB change scores for the NAMENDA XR 28 mg/AChEI-treated (combination therapy) patients compared to the patients on placebo/AChEI (monotherapy) was 2.6 units. Using an LOCF analysis, NAMENDA XR 28 mg/AChEI treatment was statistically significantly superior to placebo/AChEI.

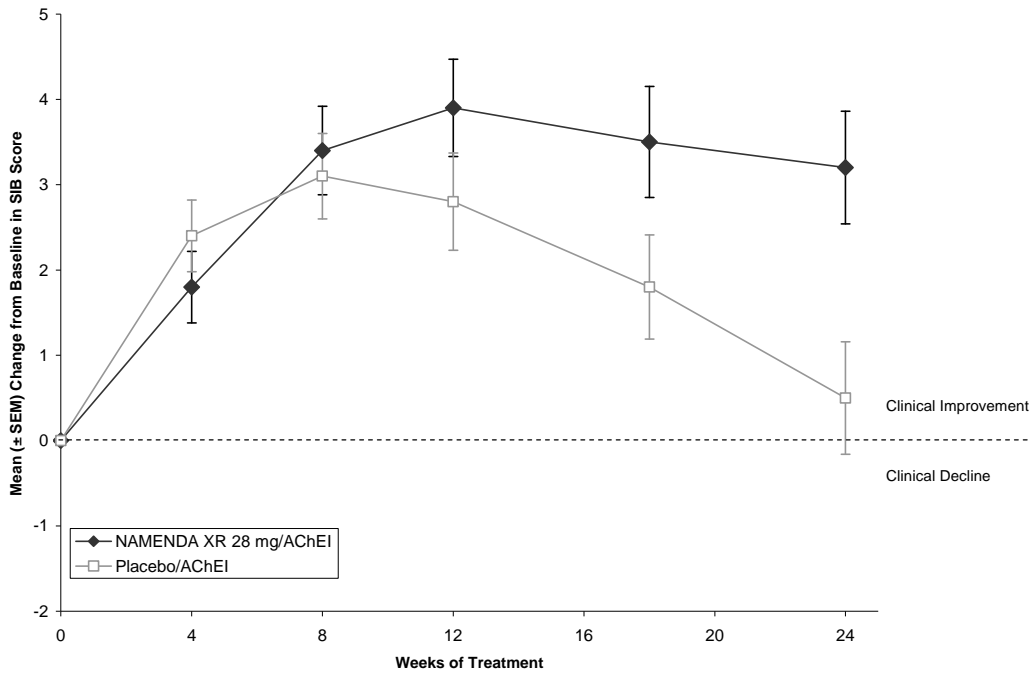


Figure 1: Time course of the change from baseline in SIB score for patients completing 24 weeks of treatment.

NDA 22525

Figure 2 shows the cumulative percentages of patients from each treatment group who had attained at least the measure of improvement in SIB score shown on the X axis. The curves show that both patients assigned to NAMENDA XR 28 mg/AChEI and placebo/AChEI have a wide range of responses, but that the NAMENDA XR 28 mg/AChEI group is more likely to show an improvement or a smaller decline.

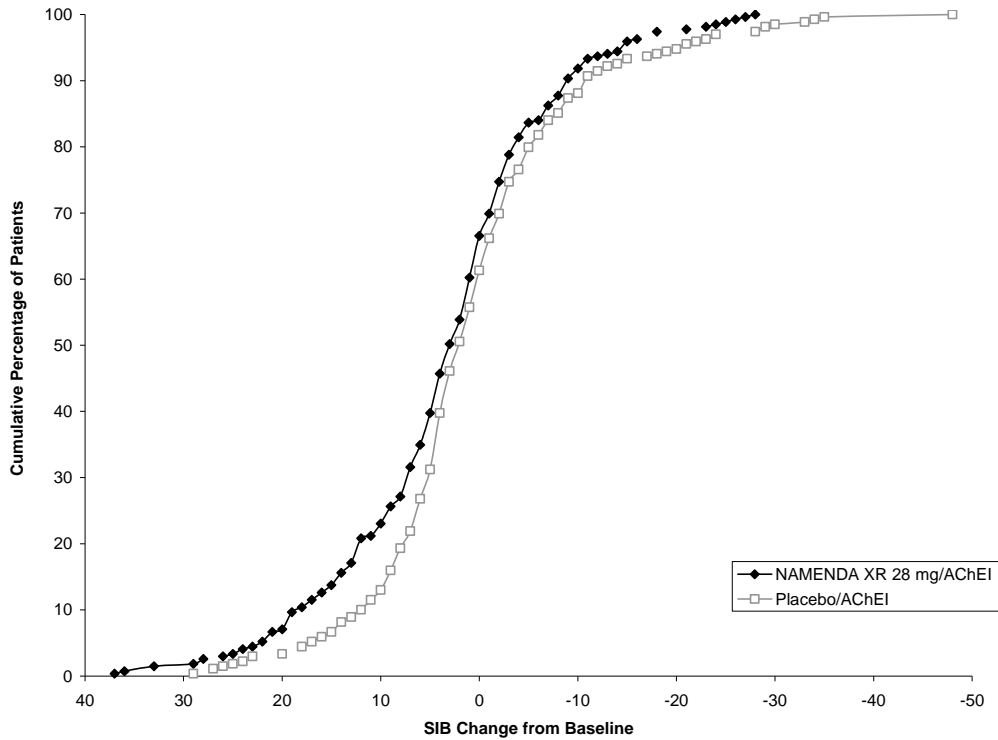


Figure 2: Cumulative percentage of patients completing 24 weeks of double-blind treatment with specified changes from baseline in SIB scores.

NDA 22525

Figure 3 shows the time course for the CIBIC-Plus score for patients in the two treatment groups completing the 24 weeks of the study. At 24 weeks of treatment, the mean difference in the CIBIC-Plus scores for the NAMENDA XR 28 mg/AChEI-treated patients compared to the patients on placebo/AChEI was 0.3 units. Using an LOCF analysis, NAMENDA XR 28 mg/AChEI treatment was statistically significantly superior to placebo/AChEI.

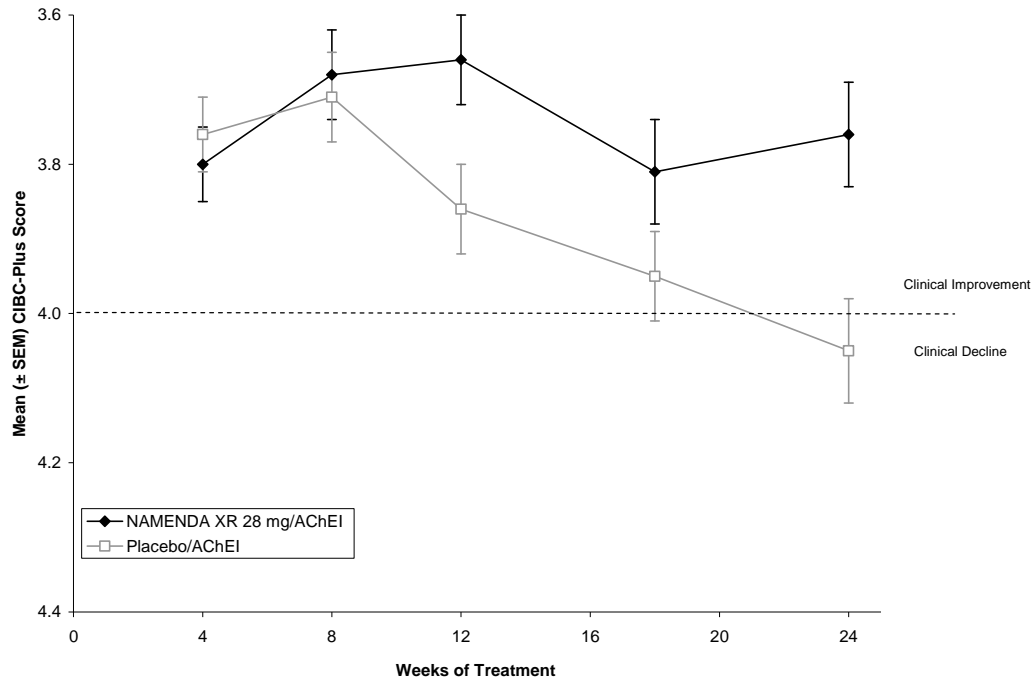


Figure 3: Time course of the CIBIC-Plus score for patients completing 24 weeks of treatment.

NDA 22525

Figure 4 is a histogram of the percentage distribution of CIBIC-Plus scores attained by patients assigned to each of the treatment groups who completed 24 weeks of treatment.

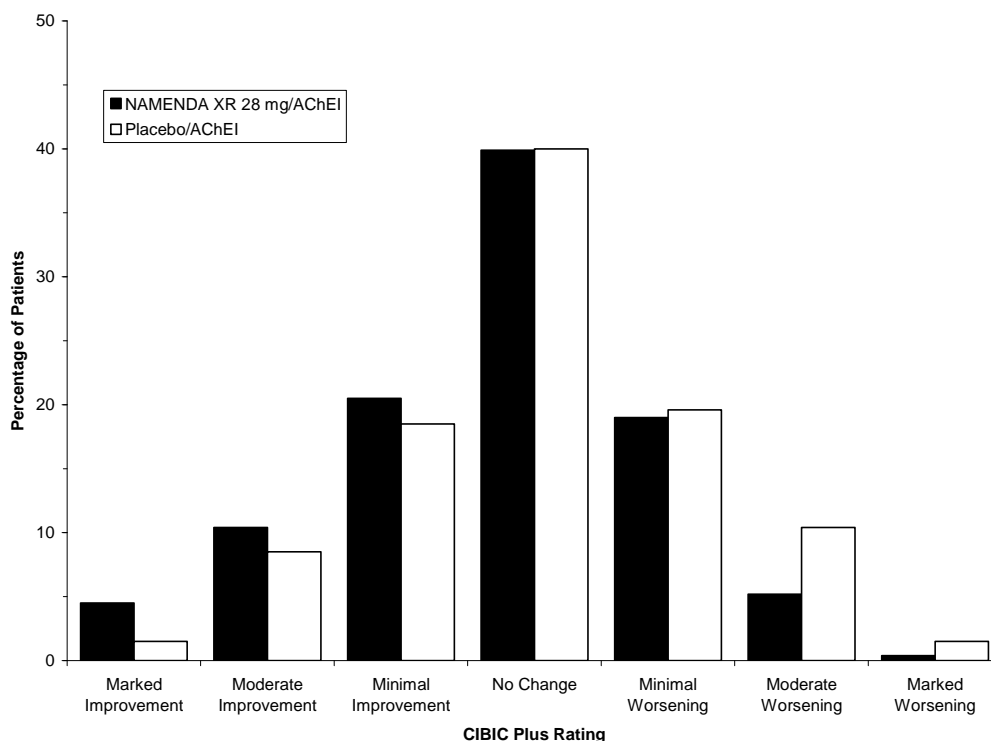


Figure 4: Distribution of CIBIC-Plus ratings at week 24.

16 HOW SUPPLIED/STORAGE AND HANDLING

7 mg Capsule:

Yellow opaque capsule, with “FLI 7 mg” black imprint.

Bottle of 30: NDC# 0456-3407-33

14 mg Capsule:

Yellow cap and dark green opaque capsule with “FLI 14 mg” black imprint on the yellow cap.

Bottle of 30: NDC# 0456-3414-33

Bottle of 90: NDC# 0456-3414-90

10 x 10 Unit Dose: NDC# 0456-3407-63

21 mg Capsule:

White to off-white cap and dark green opaque capsule, with “FLI 21 mg” black imprint on the white to off-white cap.

Bottle of 30: NDC# 0456-3421-33

28 mg Capsule:

Dark green opaque capsule, with “FLI 28 mg” white imprint.

Bottle of 30: NDC# 0456-3428-33

Bottle of 90: NDC# 0456-3428-90

10 x 10 Unit Dose: NDC# 0456-3428-63

Titration Pack:

NDC# 0456-3400-29

Contains 28 capsules (7 x 7 mg, 7 x 14 mg, 7 x 21 mg, 7 x 28 mg)

NDA 22525

Storage

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

To assure safe and effective use of NAMENDA XR, the information and instructions provided in the patient information section should be discussed with patients and caregivers.

Patients and caregivers should be instructed to take NAMENDA XR only once per day, as prescribed.

Patients and caregivers should be instructed that NAMENDA XR capsules be swallowed whole. Alternatively, NAMENDA XR capsules may be opened and sprinkled on applesauce and the entire contents should be consumed. The capsules should not be divided, chewed or crushed.

Patients and caregivers should be advised that the product may cause headache, diarrhea and dizziness.

Manufactured for:

Forest Pharmaceuticals, Inc.
Manufactured by:
Forest Laboratories Ireland Ltd
Licensed from Merz Pharmaceuticals GmbH
Issued [06.2010]

NDA 22525

PATIENT INFORMATION

NAMENDA XR [Nuh-MEN-dah Eks-Are] (memantine hydrochloride) Extended Release Capsules

What is NAMENDA XR and what is it used for?

NAMENDA XR belongs to a class of substances called NMDA antagonists. It is used for the treatment of patients with Alzheimer's disease.

Do not take NAMENDA XR in the following cases:

If you know that you are allergic (hyper-sensitive) to memantine (the active substance in NAMENDA XR) or to any of the other ingredients of NAMENDA XR (see *Description (11)*).

Take special care with NAMENDA XR if:

- You have, or ever had seizures.
- You have, or ever had difficulty passing urine.

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

NAMENDA XR with food and drink:

NAMENDA XR may be taken with or without food. NAMENDA XR capsules may be opened and sprinkled on applesauce before swallowing, but the contents of the entire capsule should be taken and the dose should not be divided. Except when opened and sprinkled on applesauce, NAMENDA XR capsules must be swallowed whole and never crushed, divided or chewed (see *Dosage and Administration (2)*).

NAMENDA XR and older people:

NAMENDA XR can be used by patients over the age of 65, as well as by patients with Alzheimer's Disease who are aged 65 years or younger.

NAMENDA XR and children:

The use of NAMENDA XR in children is not recommended.

Pregnant women:

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

Breast-feeding mothers:

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

Taking other medicines:

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

How to use NAMENDA XR:

NDA 22525

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

How to start treatment:

Treatment begins at a low dose (7 mg, once a day) and is gradually increased until the target dose (28 mg, once a day) is reached. To be effective, NAMENDA XR must be taken correctly, according to the following schedule:

Week 1: Start on Day 1

Take one 7 mg capsule each day.

Week 2: Start on Day 8

Take one 14 mg capsule each day.

Week 3: Start on Day 15

Take one 21 mg capsule each day.

Week 4: Start on Day 22

Take one 28 mg capsule each day.

Once the target dose (28 mg, once a day) has been reached, you can continue with that daily schedule unless told otherwise by your healthcare professional. (For patients with severe renal impairment, 14 mg once a day is the recommended dose.)

During the course of treatment, your healthcare professional may change the dose to suit your individual needs.

If you are currently taking another formulation of memantine, talk to your healthcare professional about how to switch to NAMENDA XR.

What to do if you take more NAMENDA XR capsules than you should:

If you accidentally take more NAMENDA XR capsules than you should, inform your healthcare professional that you have accidentally taken more NAMENDA XR than you should have. You may require medical attention. Some people who have accidentally taken too much memantine have experienced dizziness, unsteadiness, weakness, tiredness, confusion, as well as other symptoms.

If you forget to take NAMENDA XR:

If you forget to take one dose of NAMENDA XR, do not double-up on your next dose. Take only your next dose as scheduled.

If you have forgotten to take NAMENDA XR for several days, do not take the next dose until you have talked to your healthcare professional.

NDA 22525

Possible side effects:

Like all medicines, NAMENDA XR can cause side effects, although not everyone gets them.

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

The most common side effects in patients taking NAMENDA XR were headache, diarrhea and dizziness.

How to store NAMENDA XR:

Do not use NAMENDA XR after the expiration date shown on the carton and bottle.

Store at 25°C (77°F).

Do not use any capsules of NAMENDA XR that are damaged or show signs of tampering.

Keep NAMENDA XR out of the reach and sight of children and pets.