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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Memantine Hydrochloride Extended-release Capsules safely and effectively. See full prescribing information for Memantine Hydrochloride Extended-release Capsules.

MEMANTINE hydrochloride extended-release capsule, for oral use
Initial U.S. Approval: 2003

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

Dosage and Administration, Recommended Dosing (2.1) 9/2014

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

Memantine hydrochloride extended-release capsules are an NMDA receptor antagonist indicated for the treatment of moderate to severe dementia of the Alzheimer's type (1)

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

- The recommended starting dose of memantine hydrochloride extended-release capsules are 7 mg once daily; the dose should be increased in 7 mg increments to the recommended maintenance dose of 28 mg once daily; the minimum recommended interval between dose increases is one week (2.1)
- Patients with severe renal impairment: the recommended maintenance dose of memantine hydrochloride extended-release capsules is 14 mg once daily (2.3)

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

Memantine hydrochloride extended-release capsule is available as an extended-release capsule in the following strengths: 7 mg, 14 mg, 21 mg, 28 mg (3)

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

Memantine hydrochloride extended-release is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation (4)

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

Conditions that raise urine pH may decrease the urinary elimination of memantine resulting in increased plasma levels of memantine (5.1, 7.1)

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

The most commonly observed adverse reactions occurring at a frequency of at least 5% and greater than placebo with administration of memantine hydrochloride extended-release capsules 28 mg/day were headache, diarrhea and dizziness (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharmaceuticals, Inc. at 1-800-399-2561 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 01/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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 memantine hydrochloride extended-release capsules shown to be effective in a controlled clinical trial is 28 mg once daily.

The recommended starting dose of memantine hydrochloride extended-release capsules is 7 mg once daily. The dose should be increased in 7 mg increments to the recommended maintenance dose of 28 mg once daily. The minimum recommended interval between dose increases is one week. The dose does not need to be increased if the previous dose has been well tolerated. The maximum recommended dose is 28 mg once daily.

Memantine hydrochloride extended-release capsules can be taken with or without food. Memantine hydrochloride extended-release capsules can be taken intact or may be opened, sprinkled on applesauce, and thoroughly consumed. The entire contents of each memantine hydrochloride extended-release capsule should be consumed; the dose should not be divided.

Except when opened and sprinkled on applesauce, as described above, memantine hydrochloride extended-release capsules should be swallowed whole. Memantine hydrochloride extended-release capsules should not be divided, chewed, or crushed.

If a patient misses a single dose of memantine hydrochloride extended-release capsules, that patient should not double up on the next dose. The next dose should be taken as scheduled. If a patient fails to take memantine hydrochloride extended-release capsules for several days, dosing may need to be restarted at lower doses and titrated as described above.

2.2 Switching from Memantine hydrochloride Tablets to Memantine hydrochloride Extended-Release Capsules

Patients treated with memantine hydrochloride tablets may be switched to memantine hydrochloride extended-release capsules as follows:

It is recommended that a patient who is on a regimen of 10 mg twice daily of memantine hydrochloride tablets be switched to memantine hydrochloride extended-release 28 mg once daily capsules the day following the last dose of 10 mg memantine hydrochloride tablets. 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 memantine hydrochloride tablets be switched to memantine hydrochloride extended-release 14 mg once daily capsules the day following the last dose of 5 mg memantine hydrochloride tablets.

2.3 Dosing in Patients with Renal Impairment

In patients with severe renal impairment (creatinine clearance of 5 – 29 mL/min, by Cockcroft-Gault equation), the recommended maintenance dose (and maximum recommended dose) is 14 mg/day (see *CLINICAL PHARMACOLOGY 12.3*).

3 DOSAGE FORMS AND STRENGTHS

Each extended-release capsule contains: 7 mg, 14 mg, 21 mg or 28 mg of memantine hydrochloride.

- 7 mg: Size "4" hard gelatin white capsule with yellow opaque cap and yellow opaque body, with black imprint "LU" on cap and "D57" on body.
- 14 mg: Size "4" hard gelatin capsule with yellow opaque cap and dark green opaque body, with black imprint "LU" on cap and "D58" on body.
- 21 mg: Size "4" hard gelatin capsule with white opaque cap and dark green opaque body, with black imprint "LU" on cap and "D59" on body.
- 28 mg: Size "2" hard gelatin dark green capsule with black imprint "LU" on cap and "D60" on body.

4 CONTRAINDICATIONS

Memantine hydrochloride extended-release is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Genitourinary Conditions

Conditions that raise urine pH may decrease the urinary excretion of memantine resulting in increased plasma levels of memantine (see DRUG INTERACTIONS *7.1*).

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Memantine hydrochloride extended-release was evaluated in a double-blind placebo-controlled trial in which a total of 676 patients with moderate to severe dementia (the Alzheimer's type [DAT] patients) on memantine hydrochloride extended-release capsules 28 mg/day and 336 patients on placebo) were treated for 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.

Adverse Reactions Leading to Discontinuation

In the placebo-controlled clinical trial of memantine hydrochloride extended-release, the proportion of patients in the memantine hydrochloride extended-release capsules group and the placebo group who discontinued treatment due to adverse reactions was 9% and 6%, respectively. The most common adverse reaction that led to treatment discontinuation in the memantine hydrochloride extended-release group was dizziness, at a rate of 1.5%.

Most Common Adverse Reactions

The two 1 commonly observed adverse reactions seen in patients administered memantine hydrochloride extended-release in the controlled clinical trial, defined as those occurring at a frequency of at least 5% in the memantine hydrochloride extended-release group and at a frequency higher than placebo, were headache, diarrhea and dizziness.

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

Table 1: Adverse reactions observed with a frequency of ≥1% in the memantine hydrochloride extended-release capsules group and at a rate greater than placebo

Adverse reaction	*Placebo (n = 336)* %	*Memantine Hydrochloride Extended-Release Capsules 28mg (n = 340)* %
Gastrointestinal Disorders		
Diarrhea	4	5
Constipation	1	3
Abdominal pain	1	2
Vomiting	1	2
Infections and infestations		
Influenza	3	4
Investigations		
Weight, decreased	1	3
Musculoskeletal and connective tissue disorders		
Back pain	1	3
Nervous system disorders		
Headache	8	8
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

Seizure

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of memantine. 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. These reactions are:

Blood and Lymphatic System Disorders

agranulocytosis, leukopenia (including neutropenia), pancytopenia, thrombocytopenia, thrombotic thrombocytopenic purpura.

Cardiac Disorders

cardiac failure congestive.

Gastrointestinal disorders

pancreatitis.

Hepatobiliary Disorders

hepatitis.

Psychiatric Disorders

confusional elevation.

Renal and Urinary Disorders

acute renal failure (including increased creatinine and renal tract fatigue).

Skin Disorders

Stevens Johnson syndrome.

7 DRUG INTERACTIONS

7.1 Drugs That Make the Urine Alkaline

The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alkalinization of urine shifts towards the alkaline condition may cause a accumulation of the drug with a possible increase in adverse effects. Urine pH is a function of 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.

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

The combined use of memantine hydrochloride extended-release with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) has not been systematically evaluated and such use should be approached with caution.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of memantine in pregnant women. Memantine hydrochloride extended-release 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/m²basis).

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 9 of gestation through the postpartum period. The no-effect dose for these effects was 6 mg/kg, which is 2 times the MRHD on a mg/m²basis.

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 hydrochloride extended-release is administered to a nursing mother.

8.4 Pediatric Use

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

Additional information describing a clinical study in which efficacy was not demonstrated in patients 8 to 12 years old is approved for Forest Laboratories' memantine IR extended-release capsules product. However, due to Forest Laboratories' marketing exclusivity rights, this drug product is not labeled with that pediatric information.

In a juvenile animal study, male and female juvenile rats were administered memantine (1, 10, and 40 mg/kg/day) starting on postnatal day (PND) 14 through PND 70. Delays in sexual maturation and decreases in body weight gain were noted in male and female rats at doses ≥ 10 mg/kg/day. Memantine induced neuronal vacuoles in several areas of the brain on PND 18 and 17 at doses ≥ 10 mg/kg/day. Behavioral toxicity (decreasing percent of auditory startle habituation) was noted for animals in the 40 mg/kg/day dose group. The 3 mg/kg/day dose was considered the No-Observed-Adverse-Effect-Level (NOAEL) for this study.

In a second juvenile rat toxicity study, male and female juvenile rats were administered memantine (1, 3, 6, 18, 30, and 40 mg/kg/day) starting on postnatal day (PND) 7 through PND 70. Due to early memantine-related mortality, the 30 and 40 mg/kg/day dose groups were terminated without further evaluation. Memantine induced apoptotic or neuronal degeneration in several areas of the brain on PND 6, 18, and 17 at a dose of 18 mg/kg/day. The NOAEL for apoptotic and neuronal degeneration was 6 mg/kg/day. Behavioral toxicity (effects on motor activity, auditory startle habituation, and learning and memory) was noted at doses ≥ 3 mg/kg/day during treatment, but was not seen after drug discontinuation. Therefore, the 1 mg/kg/day dose was considered the NOAEL for the neurobehavioral effect in this study.

8.5 Geriatric Use

The majority of people with Alzheimer's disease are 65 years and older. In the clinical study of memantine HCl extended-release, the mean age of patients was approximately 77; over 9 % of patients were 85 years and older, 67% were 75 years and older, and 14% were at or above 85 years of age. The efficacy and safety data presented in the clinical trials section were obtained from these patients. There were no clinically meaningful differences in most adverse reactions reported by patient groups ≥ 65 years old and < 65 years old.

8.6 Renal Impairment

No dosage adjustment is needed in patients with mild or moderate renal impairment. A dosage reduction is recommended in patients with severe renal impairment (see *DOSAGE AND ADMINISTRATION 2.3*) and *CL INICAL PHARMACOLOGY (12.3)*.

8.7 Hepatic Impairment

No dosage adjustment is needed in patients with mild or moderate hepatic impairment. Memantine hydrochloride extended-release was not studied in patients with severe hepatic impairment (see *CL INICAL PHARMACOLOGY (12.3)*).

10 OVERDOSAGE

Signs and symptoms: most often accompanying overdosage 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, stupor, hallucinations, confusion, coma, dizziness, ECG changes, increased blood pressure, lethargy, loss of consciousness, psychosis, restlessness, slowed movement, tremor, 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, slurred speech, and agitation, but subsequently recovered.

One patient presenting in a memantine hydrochloride extended-release clinical trial unintentionally took 1 2 mg of memantine hydrochloride extended-release daily for 31 days and experienced an elevated serum uric acid, elevated serum alkaline phosphatase, and an platelet count. Fatal outcomes have been very rarely been reported with memantine, and the relationship to memantine was 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 case 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

Memantine hydrochloride extended-release is an orally active NMDA receptor antagonist. The chemical name for memantine hydrochloride is 1-amino-3,5-dimethylhexacyclene hydrochloride with the following structural formula:

The molecular formula is $C_{12}H_{21}NHCl$ and the molecular weight is 215.76. Memantine hydrochloride occurs as a free white to off-white powder and is soluble in water.

Memantine hydrochloride extended-release capsules are supplied for oral administration as 7, 14, 21, and 28 mg capsules. Each capsule contains extended release beads with the labeled amount of memantine hydrochloride and the following inactive ingredients: cocoa starch, diyl oil lakes, gelatin, hypromellose, sucrose, talc, titanium dioxide and triethyl citrate in hard gelatin capsules. Addition ly, 7 mg strength capsules contain D&C Ye low #10 and FD&C Red #40; 14 mg strength capsules contain D&C Yel low # 10, FD&C Blue #1, FD&C Red #40 and iron oxide yellow; 21 mg and 28 mg strength capsules contain FD&C Blue #1 and iron oxide yellow. The capsules are printed with edible ink containing black iron oxide, potassium hydroxide, propylene glycol and shellac.

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 also has low to negligible affinity for GABA, benzodiazepine, dopamine, adrenergic, histamine and glycine receptors and for voltage-dependent Ca^{2+}, Na^{+}, or K^{+} channels. Memantine also showed antagonistic effects at the $5HT_3$ receptor with a potency similar to that for the NMDA receptor and blocked nicotinic acetylcholine receptors with one-tenth to one tenth the potency.

In vivo 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 terminal elimination half-life of about 60 to 80 hours. In a study comparing 28 mg once daily memantine hydrochloride extended-release to 10 mg twice daily memantine hydrochloride tablets, the C_{max} and AUC_{0-24} in our cases 49% and 35% higher for the XR dosage regimen, respectively.

Absorption

After multiple dose administration of memantine hydrochloride extended-release, memantine peak concentrations occur around the 8 hours post-dose. There is no difference in the absorption of memantine hydrochloride extended-release when the capsule is taken intact or when the contents are sprinkled on applesauce.

There is no difference in exposure, based on C_{max} or AUC_{τ}, for memantine hydrochloride extended-release whether that dosage subject is administered with food or on an empty stomach. However, peak plasma concentrations are achieved about 8 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 to 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.

MEMANTINE hydrochloride extended-release capsule, for oral use
2339990

(b) (4)

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Elimination

Memantine is excreted predominantly in the urine, unchanged, and has a terminal elimination half-life of about 60 to 80 hours. About 48% of administered drug is excreted unchanged in urine; the remainder is considered prior rly to three polar metabolites, which possess minimal NMDA receptor antagonistic activity; the N-glucuronide conjugate, dihydroxy memantine, and 1-nitroso-dimethylated 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.

Specific Populations

Elder y:

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

Gender:

Following multiple dose administration of memantine HCl 20 mg daily, females exhibit about 40% higher exposure than males, but there was no difference in exposure when body weight was taken into account.

Renal Impairment

Memantine pharmacokinetics were evaluated following single oral administration of 20 mg memantine HCl in 8 subjects with mild renal impairment (creatinine clearance, CLcr, > 50 to 80 mL/min), 8 subjects with moderate renal impairment (CLcr 30 to 49 mL/min), 7 subjects with severe renal impairment (CLcr 5 to 29 mL/min) and 8 healthy subjects (CLcr > 80 mL/min) matched as closely as possible by age, weight and gender to the subjects with renal impairment. Mean AUC_{∞} increased by 4%, 60%, and 1 0% in subjects with mild, moderate, and severe renal impairment, respectively, compared to healthy subjects. The terminal elimination half-life increased by 8%, 41%, and 95% in subjects with mild, moderate, and severe renal impairment, respectively, compared to healthy subjects.

Hepatic Impairment

Memantine pharmacokinetics were evaluated following the administration of single oral dose of 20 mg in 8 subjects with moderate hepatic impairment (Chi-Child-Pugh Class B, score 7 to 9) and 8 subjects who were age-, gender-, and weight-matched to the hepatically-ing ired 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 6% in subjects with moderate hepatic impairment as compared with healthy subjects.

Drug-Drug Interactions

Use with Cholinesterase Inhibitors:

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

Effect of Memantine on the Metabolism of Other Drugs:

In vitro studies using human cytochrome 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 enzymes 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 carbamazepine, ranitidine, hydrochlorothiazide, glyburide, sulfamethoxazole/trimethoprim, and oral contraceptives. Memantine did not affect the pharmacokinetics of the CYP450 substrate ranitidine or its metabolite hydroxyranitidine. Furthermore, memantine did not affect the pharmacokinetics or pharmacodynamics of glyburide. Memantine did not modify the serum glucose lowering effect of glucosamine, indicating the absence of a pharmacodynamic interaction.

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.

12 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/m²basis). The same also no evidence of carcinogenicity in rats or fly dosed 1 up to 40 mg/kg/day for 71 weeks (a basis fly 20 mg/kg/day (4 and 7 times the MRHD on a mg/m²basis, 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 cytogenetic assay for chromosome damage in rats, and the in vivo mouse micronucleus assay. The tests were equivocal in an in vitro gene mutation assay using Chinese hamster V79 cells.

No impairment of fertility or reproduction performance was seen in rats administered up to 8 mg/kg/day (8 times the MRHD on a mg/m²basis) 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 and/or Pharmacology

Memantine induced neuronal lesions (vacuolization and necrosis) in the cerebrum and pyriform cortex in rats, 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 20 mg/day) on a mg/m²basis.

In acute and repeat-dose neurotoxicity tests in female rats, oral administration of memantine and donepezil in combination resulted in increased incidence, severity, and distribution of neurodegeneration compared with memantine alone. The no-effect level of the combination was associated with clinically exaggerated plasma memantine and donepezil exposures.

The relevance of these findings to humans is unknown.

14 CLINICAL STUDIES

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

24-week Study of Memantine Hydrochloride Extended-Release 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 48 to 97 years. Approximately 72% of patients were female and 94% were Caucasian.

Study Outcome Measures

The effectiveness of memantine hydrochloride extended-release capsules 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 memantine hydrochloride extended-release to improve cognitive performance was assessed with the Severe Impairment Battery (SIB), a new 6 item instrument that has been validated for the evaluation of cognitive function in patients with moderate to severe dementia. The SIB assesses extended 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 memantine hydrochloride extended-release to produce an overall clinical effect was assessed using a Clinician's Interview-Based Impression of Change that required the use of caregiver information, the CIBIC-Plus. The CIBIC-Plus is not a single instrument and is not a standardized instrument like the ADAS-Cog or SIB. Clinical trials for investigational drugs have used a variety of CIBIC formats, each different in terms of depth and structure. In each, results from a CIBIC-Plus reflect a blend 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 results in this trial used a structured interview based on a comprehensive evaluation of baseline and subsequent time-points of four domains: general 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 observations 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 on 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.

Study Results

In this study, 677 patients were randomized to one of the following 3 treatments: memantine hydrochloride extended-release capsules 28 mg/day or placebo while all receiving an AChEI (either donepezil, galantamine, or rivastigmine).

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 over up to the 24 weeks of the study. 1 24 weeks of treatment, the mean difference in the SIB change scores for the memantine hydrochloride extended-release capsules 28 mg/AChEI treated (combination therapy) patients compared to the patients on placebo/AChEI (monotherapy) was 2.8 units. Using an LOCF analysis, memantine hydrochloride extended-release capsules 28 mg/AChEI treatment was statistically significantly superior to placebo/AChEI.

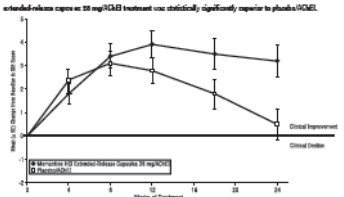

Figure 1: Time course of the change from baseline in SIB score for patients comp ating 24 weeks of treatment.

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

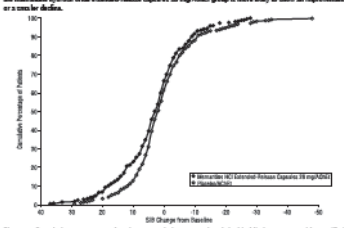

Figure 2: Cumulative percentage of patients completing 24 weeks of double-blind treatment with specified changes from baseline in SIB scores.

Figure 3 shows the time course for the CIBI C-P ics 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 memantine hydrochloride extended-release capsules 28 mg/AChEI treated patients compared to the patients on placebo/AChEI was 0.3 units. Using an LOCF analysis, memantine hydrochloride extended-release capsules 28 mg/AChEI treatment was statistically significantly superior to placebo/AChEI.

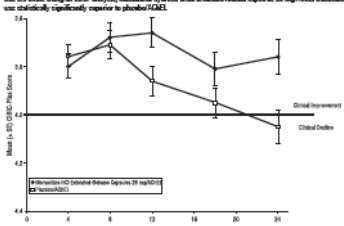

Figure 3: Time course of the CIBIC-Plus score for patients completing 24 weeks of treatment.

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

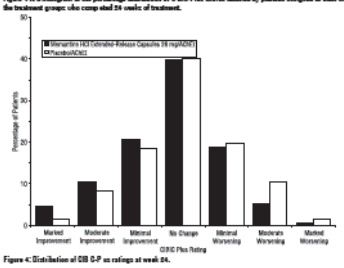

Figure 4: Distribution of CIB C-P ics ratings at week 24.

16 HOW SUPPLIED/STORAGE AND HANDLING

7 mg Capsule
Size "4" hard gelatin yellow capsule with yellow opaque cap and yellow opaque body, with black imprint "LU" on cap and "Ox " on body.

Bottle of 30:	NDC 66 30-240-08
Bottle of 90:	NDC 66 30-240-09

14 mg Capsule
Size "2" hard gelatin capsule with yellow opaque cap and dark green opaque body, with black imprint "LU" on cap and "Ox " on body.

Bottle of 30:	NDC 66 30-247-08
Bottle of 90:	NDC 66 30-247-09
Blister of 10 X 10 Unit-Dose:	NDC 66 30-247-13

21 mg Capsule
Size "0" hard gelatin capsule with white opaque cap and dark green opaque body, with black imprint "LU" on cap and "Ox " on body.

Bottle of 30:	NDC 66 30-248-08
Bottle of 90:	NDC 66 30-248-09

28 mg Capsule
Size "3" hard gelatin dark green capsule with black imprint "LU" on cap and "Ox " on body.

Bottle of 30:	NDC 66 30-249-08
Bottle of 90:	NDC 66 30-249-09
Blister of 10 X 10 Unit-Dose:	NDC 66 30-249-13

Storage
Store at 25°C (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).

- To assure safe and effective use of memantine hydrochloride extended-release, the information and instructions provided in the patient information section should be discussed with patients and caregivers.
- Instruct patients and caregivers to take memantine hydrochloride extended-release only once per day, at approx imat.
- Instruct patients and caregivers that memantine hydrochloride extended-release capsules be swallowed whole. Alternatively, memantine hydroch oride extended-release capsules may be opened and sprinkled on applesauce and the entire contents chew d the consumed. The capsules should not be divided, chewed or crushed.
- Warn patients not to use any capsules of memantine hydrochloride extended-release that are damaged or show signs of tampering.
- If a patient misses a single dose of memantine hydrochloride extended- release, that patient should not double up on the next dose. The next dose should be taken at schedule ed. If a patient fails to take memantine hydrochloride extended- release for several days, dosing should not be resumed without consulting that patient's healthcare professional.
- Advise patients and caregivers that memantine hydrochloride extended-release may cause headache, diarrhea, and dizziness.

Manufactured for:
Lupin Pharmaceuticals, Inc.
Baltimore, Maryland 21202
United States

Manufactured by:
Lupin Limited
Pithampur (M.P.) – 454 775
India

January 20 6 ID#: 3260 0

PATIENT INFORMATION

Memantine Hydrochloride Extended-release Capsules
[mem-MAN teen HYE-d ox-RLOR-ide]

Rx Only

Read this Patient Information that comes with memantine hydrochloride extended-release capsules before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is memantine hydrochloride extended-release capsules?

Memantine hydrochloride extended-release capsules is a prescription medicine used for the treatment of moderate to severe dementia in people with Alzheimer's disease. Memantine hydrochloride extended-release capsuls belongs to a class of medicines called NMDA (N-methyl-D-aspartate) inhibitors.

It is not known if memantine hydroch oride extended-release capsules is safe and effective in children.

Who should not take memantine hydrochloride extended-release capsules?

Do not take memant ne hydroch oride extended-release capsules if you are a large to memantine or any of the other ingredients in memantine hydrochloride extended-release capsules. See the end of this leaflet for a comp ete list of ingredients in memantine hydrochloride extended-release capsules.

What shou d I tell my doctor before taking memantine hydrochloride extended-release capsules?

Before you take memantine hyd och oride extended-release capsules, tell your doctor if you:

- have or have had seizures
- have or have had problems passing urine
- have or have kidnbladder or kidney problems
- have liver problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if memantine hydrochloride extended-release capsules will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if memantine hydrochloride extended-release capsules passes into your breast milk. You and your doctor should decide if you will take memantine hydrochloride extended- release capsules or breastfeed.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Taking memantine hydrochloride extended-release capsules with certain other medicines may affe t each other. Taking memantine hydrochloride extended-release capsules with other medicines can cause serious side e fects.

Especially tell your doctor if you take:

- other NMDA antagonists such as amantadine, ketamine, and dextromethorphan
- medicines that make your urine alkaline such as carbonic anhydrase inhibitors and sodium bicarbonate

Ask your doctor or pharmacist for a list of these medicines, if you are not sure.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How shou d I take memantine hydrochloride extended-release capsules?

- Your doctor will tell you how much memantine hydrochloride extended-release capsules to take and when to take it.
- Your doctor may change your dose if needed.
- Memantine hydrochloride extended-re ease capsules may be taken with food or without food.
- Memantine hydroch oride extended-release capsules may be opened and sprinkled on applesauce before you swallow, but the contents of the entire capsule should be taken and the dose should not be divided. Except when opened and sprinkled on applesauce, memantine hydrochloride extended-re ease capsules must be swallowed whole and never crushed, divided or chewed.
- Do not use any capsules of memantine hydrochloride extended-release capsules that are damaged or show signs of tampering.
- If you are currently taking another formulation of memantine, talk to your healthcare professional about how to switch to memantine hydrochloride extended-release capsules.
- If you forget to take one dose of memantine hydroch oride extended-release capsules, do not double up on the next dose. You should take only the next dose as scheduled.
- If you have forgotten to take memantine hydrochloride extended-re ease capsules for several days, you should not take the next dose until you talk to your doctor
- If you take too much memantine hydrochloride extended-re ease capsules: call your doctor or poison control center at 800-222- 1222 right away, or go to the nearest hospital emergency room.

What are the possible side effects of memantine hydroch oride extended-release capsules?

Memantine hydroch oride extended-release capsules may cause side effects, including:

The most common s de effects of memantine hydrochloride extended-re ease capsules include:

- headache
- diarrhea
- dizziness

These are not all the possible side effects of memantine hydroch oride extended-release capsules. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice abo t side effects. You may report side effects to FDA at 1-800FDA-1088. You may a so report side effects to Lupin Pharmaceuticals, Inc. at 1-800-399-3561 or visit our website at www.lupinpharmaceuticals.com

How shou d I store memantine hydrochloride extended-release capsules?

- Store memantine hydroch oride extended-release capsules at room temperature between 68 to 77°F (20 to 25°C).

What are the ingredients in memantine hydroch oride extended-release capsules?

Active ingredient: memantine hydrochloride

Inactive ingredients: maize starch, ethyl cel ulose, gelatin, hypromellose, sucrose, talc, titanium dioxide and triethyl citrate in hard gelatin capsules. Additionally, 7 mg cap sule contains D&C Yellow # 10 and FD&C Red #40; 14 mg strength capsules contain D&C Ye low # 10, FD&C Blue #1, FD&C Red #40 and iron oxide yellow; 21 mg and 28 mg cap sule capsules contain FD&C Blue #1 and iron oxide ye low. The capsules are printed with edible ink containing black iron oxide, potassium hydroxide, propylene glycol and shellac.

Keep memantine hydroch ride extended-release capsules and all medicines out of the reach of children.

General information about the s fe and e fective use of memantine hydrochloride extended-release capsules: Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not take memantine hydrochloride extended-release capsules for a condition for which it was not prescribed. Do not give memantine hydroch oride extended-re ease capsules to other people, even if they have the same condition. It may harm them.

This Patient Information leaflet summarizes the most important information about memantine hydrochloride extended-re ease capsules. If you would ike more information, talk with your doctor. You can ask your doctor or pharmacist for information about memantine hydrochloride extended-release capsules that was written for healthcare professionals.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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Pithampur (M.P.) – 454 775
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November 20 4 ID#: 326011

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