MEMANTINE HCl

MEMRY®

10 mg FILM-COATED TABLET

ANTI-DEMENTIA

FORMULATION
Each film-coated tablet contains:
Memantine hydrochloride, USP.....10 mg

PRODUCT DESCRIPTION
Memantine hydrochloride 10 mg Tablet is a white, oblong, biconvex, film-coated tablet, scored on both sides.

PHARMACOLOGY
Evidence suggests that malfunctioning of glutamatergic neurotransmission, particularly the N-methyl-D-aspartate (NMDA)-receptors, contributes to both expression of symptoms and disease progression in neurodegenerative dementia.

Memantine hydrochloride is a rapid, strongly voltage-dependent, low to moderate affinity uncompetitive (open-channel) NMDA-receptor antagonist which binds preferentially to the NMDA receptor-operated cation channels. Prolonged increased levels of glutamate in the brain of demented patients are sufficient to counter the Mg^{2+} ions voltage-dependent block of NMDA receptors and allow continuous influx of Ca^{2+} ions into cells which lead to neuronal degeneration. Studies showed that memantine hydrochloride binds more effectively than Mg^{2+} ions at the NMDA receptor, and thereby effectively blocks this prolonged influx of Ca^{2+} ions through the NMDA channels while preserving the transient physiological activation of the channels by higher concentrations of synaptically released glutamate. Thus, memantine hydrochloride modulates the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction.

There is no evidence that memantine hydrochloride prevents or slows neurodegeneration in patients with Alzheimer's disease. However, studies show that memantine hydrochloride produced statistically significant effects in preventing worsening in three endpoints (e.g., cognitive, global and functional) in patients with moderate to severe Alzheimer's disease (MMSE total score <20).

Memantine hydrochloride showed low to negligible affinity for GABA, benzodiazepine, dopamine, adrenergic, histamine, and glycine receptors and for voltage-dependent Ca^{2+}, Na^{+} or K^{+} channels. Memantine hydrochloride also showed antagonistic effects at the $5HT_3$ receptors with a potency similar to that for the NMDA receptors and blocked nicotinic acetylcholine receptors with one-sixth to one-tenth the potency. *In vitro* studies have shown that memantine hydrochloride does not affect the reversible inhibition of acetylcholinesterase by donepezil, galantamine or tacrine.

PHARMACOKINETICS
Memantine hydrochloride is completely absorbed after oral administration; absolute bioavailability is approximately 100%. It has linear pharmacokinetics over the therapeutic dose range of 10 to 40 mg. Maximum plasma concentration is achieved in 3 to 8 hours. Food tended to slow the rate but not the extent of memantine hydrochloride absorption.

Daily doses of 20 mg lead to steady-state plasma concentrations ranging from 70 to 150 ng/mL (0.5-1 μM) with large interindividual variations. A mean cerebrospinal fluid (CSF)/serum ratio of 0.52 was obtained when daily doses of 5 to 30 mg were administered. The volume of distribution is approximately 10 L/kg. Protein binding varied from 42 to 54% and no relationship was observed between plasma memantine hydrochloride concentration and protein binding.

Memantine hydrochloride undergoes partial hepatic metabolism. It is excreted mainly (60 to 80%) in its unchanged form in urine. Human metabolites are 1-amino-3-hydroxymethyl-5-methyl-adamantane, 3-amino-1-hydroxy-5,7-dimethyl-adamantane and various secondary hydroxylated not yet definitively identified memantine hydrochloride derivatives; phase II metabolism amounts for up to 10%. The known metabolites do not have any NMDA-antagonistic activity**.** *In vitro* studies have shown that memantine hydrochloride is not metabolized by cytochrome P450 (CYP) isoenzymes 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4.

Memantine hydrochloride is eliminated predominantly by the kidneys in a mono-exponential manner with a terminal half-life of 60 to 100 hours. In volunteers with normal kidney function, systemic clearance amounts to 170 mL/min. In a study on the absorption, metabolism and excretion of orally administered ^{14}C-memantine, a mean of 84% of the dose was recovered within 20 days, the majority being excreted unchanged renally**.**

Renal clearance has been shown to depend on the pH of the urine. Under alkaline conditions, the renal clearance of unchanged memantine hydrochloride is markedly reduced compared to neutral or acidic urine conditions due to tubular reabsorption of memantine hydrochloride under alkaline conditions.

Special Population:
Hepatic Impairment: After single oral dose administration of 20 mg memantine hydrochloride in subjects with moderate hepatic impairment (Child-Pugh Class B, score 7 to 9) and subjects who were age-, gender- and weight-matched to the hepatically-impaired subjects, no change in memantine hydrochloride exposure (based on C_{max} and AUC) was seen in subjects with moderate hepatic impairment as compared with healthy subjects. However, the terminal elimination half-life increased by about 16% in subjects with moderate hepatic impairment as compared with healthy subjects.

Renal Impairment: After single oral dose administration of 20 mg memantine hydrochloride in subjects with mild renal impairment (creatinine clearance, CL_{cr}, >50 to 80 mL), moderate renal impairment (CL_{cr} 30 to 49 mL/min), severe renal impairment (CL_{cr} 5 to 29 mL/min), or in healthy subjects (CL_{cr} 80 mL/min) matched as closely as possible by age, weight and gender to the subjects with renal impairment, the mean AUC_{ss}, increased by 4%, 60% or 115% in subjects with mild, moderate or severe renal impairment, respectively, compared to healthy subjects. The terminal half-life increased by 18%, 41% or 95% in subjects with mild, moderate or severe renal impairment, respectively, compared to healthy subjects.

In the elderly with impaired renal function [creatinine clearance (CL_{cr}): 50 mL/min], a significant correlation was observed between CL_{cr} and total renal clearance (CL_{tot}) of memantine hydrochloride. Total renal clearance substantially exceeded renal clearance by filtration, thus indicating that a significant part of renal clearance is due to tubular secretion processes.

INDICATION
• Used in the treatment of moderate to severe Alzheimer's disease.

DOSAGE AND ADMINISTRATION
Memantine hydrochloride can be taken with or without food.
Recommended Starting Dose: 5 mg once a day
Recommended Maximum Dose: 20 mg per day

The dose should be increased in 5 mg increments over the first four weeks of treatment reaching the recommended maintenance dose as follows:

Week	Dose
Week 1 (days 1 to 7)	5 mg once a day (half tablet in the morning)
Week 2 (days 8 to 14)	10 mg per day (half tablet in the morning and half tablet in the evening)
Week 3 (days 15 to 21)	15 mg per day (one tablet in the morning and half tablet in the afternoon or evening)
Week 4 (days 22 to 28)	20 mg per day (one tablet in the morning and one tablet in the afternoon or evening)

The minimum recommended interval between dose increases is one week.

Recommended Maintenance Dose: 20 mg per day

Hepatic Impairment:
In patients with mild or moderate hepatic impairment (Child-Pugh A and Child-Pugh B), no dosage adjustment is required. No data is available for patients with severe hepatic impairment. Administration of memantine is not recommended in patients with severe hepatic impairment.

Renal Impairment:
• **Patients with mild renal impairment (CL_{cr}: 50 to 80 mL/min):** No dosage adjustment is required in patients with mild renal impairment.

• **Patients with moderate renal impairment (CL_{cr}: 30 to 49 mL/min):** 10 mg per day

If well - tolerated after at least seven days of treatment, the dose can be increased up to 20 mg per day according to the standard titration scheme.

• **Patients with severe renal impairment (CL_{cr}: 5 to 29 mL/min):** 10 mg per day

Elderly (over 65 years old): 20 mg per day

Or, as prescribed by a physician.

CONTRAINDICATION
• Hypersensitivity to memantine hydrochloride or any ingredient of the product

WARNINGS AND PRECAUTIONS
Caution is recommended in patients with epilepsy, past history of convulsions or patients with predisposing factors for epilepsy**.**

Treatment with memantine hydrochloride should be initiated and supervised by a physician experienced in the diagnosis and treatment of dementia; diagnosis should be based on current guidelines. Therapy should be initiated only when a caregiver is available who will monitor patient compliance. Treatment with memantine hydrochloride should be continued only where there is a therapeutic benefit to the patient; therapeutic benefit should be reassessed on a regular basis.

The clearance of memantine hydrochloride was reduced by about 80% under alkaline urine conditions (pH 8). Thus, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Some factors that may raise urine pH may require careful patient monitoring. These factors include drastic changes in diet (e.g., from a carnivore to a vegetarian diet, or a massive ingestion of alkalizing gastric buffers), drugs (e.g., carbonic anhydrase inhibitors, sodium bicarbonate) and the clinical state of the patient (e.g., renal tubular acidosis or severe infections of the urinary tract with *Proteus* bacteria).

Moderate to severe Alzheimer's disease usually causes impairment of driving performance and compromises the ability to use machinery**.** Furthermore, memantine hydrochloride may change reactivity and therefore patients should be warned to take special care when driving a vehicle or operating heavy machinery**.**

Patients with recent myocardial infarction, uncompensated congestive heart failure (NYHA III-IV) or uncontrolled hypertension were excluded in most clinical trials. As a result, only limited data are available and patients with these conditions should be closely supervised.

Ocular toxicity
Animal studies have shown adverse effects of memantine hydrochloride on the visual system. Dietary administration of memantine hydrochloride to rats for one year was associated with abnormal lysosomal storage in ganglion cells and retinal pigment cells at systemic exposures (plasma AUC) of 10-fold the anticipated clinical exposure at the recommended dose, while administration for eight weeks was associated with lens opacity, increased corneal and lens capsular densities, and histological changes in cornea and lens at exposures (plasma AUC) of 20-fold the clinical exposure. Oral administration of memantine hydrochloride to dogs with systemic exposures (plasma AUC) of 3- to 8-fold the clinical exposure was associated with corneal clouding/opacity and baboons showed swollen lenticular fibers in the eyes after oral memantine hydrochloride for three months at less than clinical exposure.

In a 6-month double-blind, placebo-controlled clinical study, specific ophthalmological examinations including slit lamp tests did not show any ocular changes. In the following 6-month open-label extension period, 368 patients underwent eye examinations. At the end of open label treatment, the incidence of cataract (lens previously clear but unclear at end of open label treatment) was reported in 11 of 197 patients (6%) treated with memantine hydrochloride for 12 months compared with 5 of 171 patients (3%) who received placebo in the double-blind period and then memantine hydrochloride for 6 months (p=0.3059).

INTERACTIONS WITH OTHER MEDICAMENTS
• **N-methyl-D-aspartate antagonists (amantadine, ketamine and dextromethorphan):** Increased risk of CNS toxicity when memantine hydrochloride is given with NMDA antagonists. Avoid concomitant use. These compounds act at the same receptor system as memantine hydrochloride, and thus adverse drug reactions, mainly CNS-related, may be more frequent or more pronounced.

• **L-dopa, dopaminergic agonists (e.g., bromocriptine) and anticholinergics:** The mode of action suggests that the effects of these drugs may be enhanced by concomitant treatment with NMDA-antagonists such as memantine hydrochloride.

• **Barbiturates and neuroleptics:** The effects of these drugs may be reduced by memantine hydrochloride.

• **Antispasmodic agents (dantrolene or baclofen):** Concomitant administration of memantine hydrochloride with the antispasmodic agents, dantrolene or baclofen, can modify their effects and a dosage adjustment may be necessary**.**

• **Oral anticoagulants (e.g., warfarin):** Memantine hydrochloride possibly enhances the anticoagulant effect of warfarin. Close monitoring of prothrombin time or INR is advisable for patients concomitantly treated with oral anticoagulants.

• **Cimetidine, ranitidine, procainamide, quinidine, quinine, and nicotine:** May also possibly interact with memantine hydrochloride leading to a potential risk of increased plasma levels of both agents.

• **Diuretics [e.g., hydrochlorothiazide (HCTZ), triamterene (TA)]:** There may be a possibility of reduced HCTZ plasma level when memantine hydrochloride is used concomitantly**.** However, co-administration of memantine hydrochloride and HCTZ/TA did not affect the bioavailability of either memantine hydrochloride or TA; the bioavailability of HCTZ decreased by 20%.

• **Primidone:** Memantine hydrochloride possibly reduces the effects of primidone.

• **Selegiline:** Memantine hydrochloride possibly enhances the effects of selegiline.

• **Glibenclamide/metformin, donepezil and galantamine:** No relevant drug-drug interaction.

• **Effects of memantine on substrates of microsomal enzymes:** *In vitro* studies done with marker substrates of CYP450 enzymes (CYP1A2, -2A6, -2C9, -2D6, -2E1, -3A4) showed minimal inhibition of these enzymes by memantine hydrochloride. Also, *in vitro* studies indicate that at concentrations exceeding those associated with efficacy, memantine hydrochloride does not induce the cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2E1, and CYP3A4/5. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

• **PREGNANCY AND LACTATION**
Pregnancy Category B. There are no adequate and well-controlled studies of memantine hydrochloride in pregnant women. Memantine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether memantine hydrochloride is excreted in human milk. Caution should be exercised when memantine hydrochloride is administered to a breastfeeding mother**.**

• **PEDIATRIC USE**
There are no adequate and well-controlled studies on the efficacy and safety of memantine hydrochloride in any illness occurring in children.

ADVERSE EFFECTS
Body as a whole: Fatigue, pain, leg pain, fall, pallor, malaise, inflicted injury, accidental injury, aggravated condition, hernia inguinal, hernia, congenital hernia, rigors, temperature change sensation, hypothermia, influenza-like symptoms, infection (bacterial, fungal), abrasion, cyst

Cardiovascular: Hypertension, hypotension, postural hypotension, bradycardia, syncope, cardiac failure, angina pectoris, edema, peripheral edema, thrombophlebitis, atrial fibrillation, cardiac arrest, venous thrombosis/thromboembolism, hot flushes, pulse weak, cardiomegaly, ECG abnormal, heart disorder, heart murmur, aortic stenosis, arrhythmia (atrial and ventricular), bundle branch block, extrasystoles, heart block, palpitation; QT prolonged, rhythm & rate disturbance e.g., QTc prolongation, ischemic event, sudden death (e.g., myocardial infarction, tachycardia); aortic valve incompetence, coronary artery disorder, heart valve disorders, mitral insufficiency, transient ischemic attack, peripheral ischemia, thrombophlebitis, phlebitis, varicose vein, arteriosclerosis

Nervous system: Dizziness, vertigo, headache, confusion, amnesia, insomnia, sleep disorder, somnolence, hallucination, agitation, nervousness, aggressive reaction, delusion, personality disorder, emotional lability, abnormal gait, depression, anxiety, psychosis, apathy, paranoid reaction, abnormal thinking, abnormal crying, paroniria, delirium, depersonalization, impaired concentration, excitation/mania, cerebrovascular accident, cerebral hemorrhage, ataxia, paresthesia, convulsions, extrapyramidal disorder, tardive dyskinesia, involuntary muscle contractions, hypertonia, tremor, hyporeflexia, paralysis, sensory disturbance, speech disorder, aphasia, hypoesthesia, abnormal coordination, abnormal reflexes, hemiplegia, hyperkinesia, hypokinesia, stupor, neuralgia, ischial neuralgia, ptosis, neuropathy, neurosis, suicide attempt, apraxia, cognitive disorders, convulsions, coma, encephalopathy, dementia, Alzheimer's disease.

Gastrointestinal: Dry mouth, toothache, tooth caries, tooth disorder, gingivitis, nausea, vomiting, diarrhea, dyspepsia, abdominal pain, gastroenteritis, diverticulitis, GI hemorrhage, esophageal ulceration, gastroesophageal reflux, esophagitis, dysphagia, eructation, flatulence, gastritis, GI neoplasm benign, ulcerative stomatitis, pancreatitis, constipation, change in bowel habits, colitis, diverticulosis, hemorrhage rectum, hemorrhoids, ileus, increased stool frequency, fecal incontinence, melena

Hematologic: Anemia, leukopenia, basal cell and squamous carcinoma, malignant lymphoma, epistaxis, hematoma, hemorrhage, purpura, leukocytosis, erythrocyte sedimentation rate (ESR) increased, polycythemia, sepsis

Respiratory: Coughing, dyspnea, bronchitis, upper respiratory tract infection, pneumonia, apnea, asthma, hemoptysis, rhinitis, pulmonary embolism, asthma, atelectasis, bronchospasm, chronic obstructive pulmonary disease, laryngitis, pharyngitis, pulmonary edema, respiratory disorder, respiratory insufficiency, sinusitis

Musculoskeletal: Back pain, arthralgia, arthritis, arthrosis, bone disorder, bursitis, muscle weakness, myalgia, skeletal pain, involuntary muscle contractions, carpal tunnel syndrome

Endocrine/Metabolic: Increased alkaline phosphatase, decreased weight, anorexia, appetite increased, dehydration, hypernatremia, hyponatremia, aggravated diabetes mellitus, hyperglycemia, hypoglycemia, osteoporosis, increased/decreased libido, impotence, antidiuretic hormone disorder, hyperthyroidism, hypothyroidism, thyroid stimulating hormone (TSH) increased, blood urea nitrogen (BUN) increased, gout, hypercholesterolemia, hyperkalemia, hypokalemia, hyperlipemia, hyperuricemia, non-protein nitrogen (NPN) increased, polydipsia

Hepatic: Bilirubinemia, gamma-GT increased, hepatic enzymes increased, hepatic function abnormal, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased

Reproductive/Urogenital: Urinary incontinence, urinary tract infection, frequent micturition, dysuria, polyuria, pyuria, renal calculus, renal cyst, abnormal renal function, hematuria, urinary retention, cystitis, benign and malignant breast neoplasm, moniliasis, vaginal hemorrhage

Skin and appendages: Rash, skin ulceration, pruritus, cellulitus, eczema, dermatitis, erythematous rash, alopecia, urticaria, abscess, herpes zoster, bullous eruption, dermatitis, hyperkeratosis, melanosis, onychomycosis, skin disorder, dry skin, skin exfoliation, skin reaction isolated, sweating increased, allergic reaction

Special Senses: Cataract, conjunctivitis, macula lutea degeneration, decreased visual acuity, blepharitis, blurred vision, corneal opacity, glaucoma, conjunctival hemorrhage, eye pain, ectropion, retinal hemorrhage, xerophthalmia, diplopia, abnormal lacrimation, myopia, retinal detachment, decreased hearing, tinnitus, earache, ear disorder, otitis externa, taste perversion

OVERDOSAGE & MANAGEMENT
Signs and symptoms associated with memantine hydrochloride overdosage include agitation, confusion, ECG changes, loss of consciousness, psychosis, restlessness, slowed movement, somnolence, stupor, unsteady gait, visual hallucinations, vertigo, vomiting, and weakness.

In one case of extreme overdosage, the patient survived the intake of up to 2,000 mg memantine hydrochloride showing CNS effects (e.g., coma, diplopia and agitation) which resolved without permanent sequela.

In the event of overdosage, treatment should be symptomatic. No specific antidote for intoxication or overdose is available. Standard clinical procedures to remove active substance material, e.g., gastric lavage, carbo medicinalis (main ingredient is activated charcoal; interruption of potential entero-hepatic recirculation), acidification of urine, and forced diuresis, should be used as appropriate.

In case of signs and symptoms of general CNS overstimulation, careful symptomatic clinical treatment should be considered.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

STORAGE CONDITION
Store at temperatures not exceeding 30°C.

AVAILABILITY
Memantine HCl (Memry®) 10 mg Film-coated Tablet - PVC/Alu Blister Pack x 10's (Box of 30's) - DR-XY42967

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

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