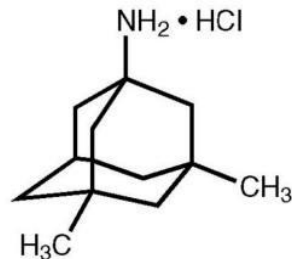


**APO-MEMANTINE TABLETS****NAME OF THE MEDICINE**

Memantine hydrochloride.

Chemical Name: 1-amino-3, 5-dimethyl-adamantane hydrochloride

Structural Formula:



Molecular Formula: C<sub>12</sub>H<sub>21</sub>N.HCl

Molecular Weight: 215.77

CAS Number: 19982-08-2 (free base)  
4110-52-1 (hydrochloride salt)

**DESCRIPTION**

Memantine hydrochloride is a colourless crystalline substance with a bitter taste. The solubility of memantine hydrochloride in water at room temperature is about 3.5%. No polymorphic forms have been detected.

Each tablet contains 10 mg or 20 mg memantine hydrochloride as the active ingredient.

The 10mg tablet also contains the following inactive ingredients: lactose, microcrystalline-cellulose, croscarmellose sodium, magnesium stearate, hypromellose, hydroxypropylcellulose, macrogol 8000 and titanium dioxide.

The 20mg tablet also contains the following inactive ingredients: microcrystalline-cellulose, croscarmellose sodium, methylcellulose, magnesium stearate, hypromellose, hydroxypropylcellulose, macrogol 8000, titanium dioxide, iron oxide red and ferric oxide yellow.

**PHARMACOLOGY****Pharmacological Actions**

There is increasing evidence that malfunctioning of glutamatergic neurotransmission, in particular at N-methyl-D-aspartate (NMDA) receptors, contributes to both expression of symptoms and disease progression in neurodegenerative dementia.

Memantine is a rapid, strongly voltage-dependent, uncompetitive NMDA receptor antagonist. Prolonged increased levels of glutamate in the brain of demented patients are sufficient to counter the voltage-dependent block of NMDA receptors by Mg<sup>2+</sup> ions and allow continuous influx of Ca<sup>2+</sup> ions into cells and ultimately neuronal degeneration. Studies suggest that memantine binds more effectively than Mg<sup>2+</sup> ions at the NMDA receptor, and thereby effectively blocks this prolonged influx of Ca<sup>2+</sup> ions through the NMDA channel whilst preserving the transient physiological activation of the channels by

higher concentrations of synaptically released glutamate. Thus memantine protects against chronically elevated concentrations of glutamate.

In animal models of disturbances in glutamatergic transmission memantine has been shown both to improve learning and to inhibit neurodegeneration at doses achieving plasma levels similar to those seen in clinical use. This in turn may explain the effect of memantine on dementia of the Alzheimer type.

At later stages of dementia, a functional deficit in glutamatergic transmission occurs due to loss of neurones bearing NMDA receptors.

In humans, memantine has not been shown to slow or reverse the neurodegenerative processes of Alzheimer's disease.

## **Pharmacokinetics**

### Absorption

In humans, complete absorption of memantine with no first pass effect was demonstrated. The absolute bioavailability is approximately 100%. Peak plasma concentration is achieved between 5 and 8 hours. Food tended to slow the rate of memantine absorption but not the extent of absorption. The tablet and drop formulations are bioequivalent.

### Distribution

Daily doses of 20 mg in humans lead to steady-state plasma concentrations ranging from 70 to 150ng/mL (0.5–1  $\mu$ M) with large interindividual variations. In healthy volunteers, the pharmacokinetics of memantine were linear over the dose range of 10 to 40 mg.

When daily doses of 5 to 30 mg were administered, a mean cerebrospinal fluid (CSF)/serum ratio of 0.52 was obtained. The inhibition constant ( $k_i$ ) of memantine at its site of action in human frontal cortex has been determined to be 0.5  $\mu$ M. In subjects receiving a daily dose of 2 x 10 mg steady-state plasma levels were reached around day 11 and varied between 0.5 and 1.0  $\mu$ M, which leads to CSF levels close to the  $k_i$  of memantine.

The volume of distribution is approximately 10 L/kg. Protein binding in humans varied from 42% to 54% and no relationship was observed between plasma memantine concentration and protein binding.

### Metabolism

In humans, memantine is excreted mainly (60–80%) 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-derivatives; phase II metabolism amounts for up to 10%. The known metabolites do not have any NMDA-antagonistic activity. In view of the minor degree of metabolism, variation with respect to polymorphic metabolism is not anticipated.

*In vitro* experiments have indicated that memantine is not metabolised by CYP isoenzymes 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and 3A4.

### Elimination

Memantine is eliminated predominantly by the kidneys in a monoexponential manner with a terminal half-life of 60 to 100 h. 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 is markedly reduced compared to neutral or acidic urine conditions. This is presumably due to tubular reabsorption of memantine under alkaline conditions.

## CLINICAL TRIALS

Two clinical trials in a population of patients suffering from moderately severe to severe dementia showed a beneficial effect of memantine treatment in comparison to placebo over a treatment period of three and six months, respectively. This benefit was measured by the patients' cognitive function, functional capacities (activities of daily living) and by clinical global status. There were no consistent differences between sexes observed in these trials.

### 6 Month Study

A 6 month multicenter, double-blind, randomised, placebo controlled study conducted in a population of patients suffering from moderately severe to severe Alzheimer's Disease (MMSE 3–14). A total of 252 outpatients of Asian American, African American and Caucasian background were included (33% male, 67% female, mean age 76 years). The dosing was 10 mg memantine b.i.d.

Outcomes included assessment of the cognitive domain (using the Severe Impairment Battery (SIB)), the global domain (using the Clinicians Interview-Based Impression of Change (CIBIC-Plus)) and the functional domain (using the modified Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL)).

The efficacy results described are from the ITT dataset (all randomised patients) with the LOCF method (last observation carried forward) as well as the OC (observed cases). Based on the OC analyses, the results of this study met the requirement of the European Union Guideline CPMP/EWP/553/95 for statistically significant improvements in the functional and global endpoints as primary evidence of clinically relevant symptomatic improvement in more advanced forms of Alzheimer's disease. An overview of the results in the most important domains of efficacy is displayed in Table 1.

**Table 1:**

#### Efficacy Results of a 6 Month Study in Patients Suffering from Alzheimer's Disease

Domain	ITT-LOCF Analysis				ITT-OC Analysis			
	Placebo (n=126)	Memantine (n=126)	Mean Difference	p value	Placebo (n=84)	Memantine (n=97)	Mean Difference	p value
<b>Cognition: SIB (score range 0-100)</b>	- 9.84 (SD 13.43)	-3.93 (SD 11.26)	5.91	<0.001	-10.16 (SD 12.66)	-4.46 (SD 11.48)	5.7	0.002
<b>Function: ADCS-ADL sev. (score range 0- 54)</b>	- 5.08 (SD 6.30)	-3.02 (SD 6.75)	2.06	0.022	-5.86 (SD 6.78)	-2.49 (SD 6.27)	3.37	0.003
<b>Global: CIBIC- plus (score range 1-7)</b>	4.73 (SD 1.07)	4.48 (SD 1.09)	0.25	0.064	4.74 (SD 1.13)	4.38 (SD 1.12)	0.36	0.025

Memantine was very well tolerated with similar frequency and type of adverse events observed with memantine compared with placebo.

### 3 Month Study

A 3 month multi-centre, double-blind, randomised, placebo-controlled study has been performed in Caucasian patients suffering from moderately severe to severe Alzheimer's disease or vascular dementia (MMSE < 10). In this study a total of 79 nursing home residents (33% male, 67% female, mean age 74 years) had Alzheimer's disease. The dosing used was 10 mg memantine daily.

Outcomes included assessment of the cognitive domain (using the cognitive subscore of the rating scale for geriatric patients (BGP)), the global domain (using the Clinical Global Impression of Change (CGI-C)) and the functional domain (using the subscore care dependency of the BGP).

Despite the small sample size, the results in all of these three domains were statistically significant in favour of memantine (see Table 2). The efficacy results described are from the ITT dataset (all randomised patients) with the LOCF method (last observation carried forward) as well as OC (observed cases).

**Table 2:****Efficacy Results for a 3 Month Study in Patients Suffering from Alzheimer's Disease**

Domain	LOCF Analysis				OC Analysis			
	Placebo (n=38)	Memantine (n=41)	Mean Difference	p value	Placebo (n=37)	Memantine (n=39)	Mean Difference	p value
<b>BGP cognitive (score range 0 to 10)</b>	-1.03	-2.00	0.97	0.007	-1.05	-2.10	1.05	0.004
<b>BGP functional (score range 0 to 46)</b>	-2.79	-5.76	2.97	0.003	-2.89	-6.05	3.16	0.002
<b>CGI-C (score range 1-7)</b>	3.47	3.15	0.32	0.002	3.46	3.08	0.38	0.005

Memantine was well tolerated, with physicians rating tolerability as 'very good' in 71% of memantine and 69% of placebo treated patients. In the remaining patients tolerability was assessed as 'good', with the exception of one memantine treated patient where it was assessed as 'moderate'.

**INDICATIONS**

Treatment of the symptoms of moderately severe to severe Alzheimer's disease (see **PHARMACOLOGY, PRECAUTIONS**).

**CONTRAINDICATIONS**

Memantine is contraindicated in patients with:

- Hypersensitivity to either the active ingredient or any of the excipients (see **DESCRIPTION**).
- A current seizure disorder or with any history of seizures.

**PRECAUTIONS****Risk of Seizures**

Memantine is contraindicated in patients with epilepsy. Caution is recommended in patients with a former history of convulsions or patients with predisposing factors for epilepsy.

**Patient Care**

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

**Ocular Toxicity**

Animal studies have reported adverse effects of memantine on the visual system. Dietary administration of memantine to rats for one year was associated with abnormal lysosomal storage in ganglion cells and retinal pigment cells at systemic exposures (plasma AUC) 10 fold anticipated clinical exposure at the recommended dose, while administration for 8 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 clinical exposure. Oral administration of memantine to dogs with systemic exposures (plasma AUC) of 3–8 fold clinical exposure was associated with corneal clouding/opacity and baboons showed swollen lenticular fibres in the eyes following oral memantine for 3 months at less than clinical exposure.

Specific ophthalmological examinations including slit lamp examinations in a 6 months clinical study with memantine did not disclose any ocular changes in the double-blind placebo-controlled treatment period. In the following 6 months 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 out of 197 patients (6%) treated with memantine for 12 months compared to 5 out of 171 patients (3%) who received placebo in the double-blind period and then memantine for 6 months ( $p=0.3059$ , Fisher's Exact Test).

### Urinary pH

Some factors that may raise urinary pH may necessitate careful monitoring of the patient. These factors include drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or a massive ingestion of alkalinising gastric buffers. Also, urine pH may be elevated by states of renal tubular acidosis (RTA) or severe infections of the urinary tract with *Proteus* bacteria.

### Renal Impairment

In patients with mildly impaired renal function (creatinine clearance 50–80 mL/min), no dosage adjustment is required. A reduction in dosage is advised for patients with moderate to severe renal impairment (see **DOSAGE AND ADMINISTRATION**).

### 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 (see **DOSAGE AND ADMINISTRATION**). Administration of memantine is not recommended in patients with severe hepatic impairment.

### Cardiovascular Disease

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

### Effects on Ability to Drive and Use Machines

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

### Effects on Fertility

Fertility was not affected by oral administration of memantine to male and female rats prior to and during mating at doses associated with respective systemic exposures (plasma AUC) of twice and 4 fold anticipated clinical exposure at the recommended dose.

### Use in Pregnancy (Category B2)

There was no evidence of teratogenicity in rats following oral administration of memantine during the period of organogenesis at estimated exposures (plasma AUC) of up to 4 fold anticipated clinical exposure at the recommended dose. There was also no teratogenicity in rats following oral administration to males prior to and during mating and to females from prior to mating to late gestation or to weaning, with respective estimated systemic exposures (plasma AUC) of twice and 4 fold anticipated clinical exposure. There was no teratogenicity in rabbits following oral administration of memantine during the period of organogenesis at doses up to 25 fold the clinical dose, based on body surface area.

### Use in Lactation

Oral administration of memantine to rats during late gestation and lactation was associated with increased post-implantation loss and transiently reduced neonatal bodyweight at estimated systemic exposures (plasma AUC) of 4 fold anticipated clinical exposure at the recommended dose. It is not known whether memantine is excreted in animal or human milk. Because of the potential for causing toxicity, memantine should be contraindicated in nursing women.

### Genotoxicity

Memantine did not show any genotoxic potential in assays for gene mutation (bacterial and mammalian cells *in vitro*) or in clastogenicity assays (human lymphocytes *in vitro* and mouse bone marrow *in vivo*).

### **Carcinogenicity**

Long term dietary administration of memantine to mice (2 years) and rats (2.5 years), with respective estimated systemic exposures of 9 fold (plasma levels) and 4–8 fold (plasma AUC) the anticipated clinical exposure at the recommended dose, did not reveal any carcinogenic potential.

### **Lactose intolerance**

The 10 mg tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take this medicine.

## **INTERACTIONS WITH OTHER MEDICINES**

### NMDA Antagonists

Concomitant use of N-methyl-D-aspartate (NMDA) antagonists such as amantadine, ketamine or dextromethorphan should be avoided. These compounds act at the same receptor system as memantine, and therefore adverse drug reactions (mainly CNS-related) may be more frequent or more pronounced. There is a risk of pharmacotoxic psychosis when memantine and amantadine are used concomitantly. Both compounds are chemically related NMDA antagonists. The same may be true for ketamine and dextromethorphan.

### Drugs Affecting the Central Nervous System

The mode of action suggests that the effects of L-dopa, dopaminergic agonists (e.g. bromocriptine), anticholinergics and amantadine on the central nervous system may be potentiated.

If barbiturates, neuroleptics, anticonvulsants, dantrolene or baclofen are being given simultaneously, their effect can be modified, possibly necessitating a dose adjustment. These recommendations are mainly based on theoretical considerations.

In *in vitro* studies, interactions with reversible acetylcholinesterase inhibitors (donepezil, tacrine) were not seen. In single dose PK studies in young healthy subjects, no relevant drug-drug interaction of memantine with donepezil was observed. Similarly, no relevant effect of memantine on the pharmacokinetics of galantamine was observed in a clinical study in young healthy subjects.

In clinical trials, clinically relevant interactions with aspirin, tocopherol, donepezil, paracetamol and chloral hydrate were not observed.

### Glyburide/Metformin

In single dose PK studies in young healthy subjects, no relevant drug-drug interaction of memantine with glyburide/metformin was observed.

### Hepatic Enzymes

Because of its low extent of metabolism by CYP450 isoenzymes, metabolic drug interactions appear unlikely. *In vitro* interaction investigations using human liver microsomes did not reveal interaction with markers of CYP 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and 3A. The only reaction slightly affected by the addition of 10 µM memantine was methimazole oxidation (marker of Ziegler's enzyme, a flavin containing monooxygenase).

### Highly Protein Bound Drugs

As memantine is bound to plasma proteins at only 42% to 54%, interactions with highly protein bound drugs (e.g. warfarin) would not be expected.

### Warfarin

In post marketing experience, isolated cases with international normalised ration (INR) increases have been reported in patients concomitantly treated with warfarin. Although no causal relationship has been established, close monitoring of prothrombin time or INR is advisable for patients concomitantly treated with oral anticoagulants.

Drugs Using the Same Renal Cationic Transport System

*In vitro* studies to examine potential interactions at renal tubular secretion sites revealed a potential competition with drugs which are secreted via the same basic cation transporter. In rat proximal and distal tubules (*in vitro*), memantine inhibited renal tubular uptake of amantadine.

Drugs such as cimetidine, ranitidine, procainamide, quinidine, quinine and nicotine that use the same renal cationic transport system as amantadine may also possibly interact with memantine leading to a potential risk of increased plasma levels.

Diuretics

The potential interaction with hydrochlorothiazide/triamterene in humans was also studied. Elderly volunteers received hydrochlorothiazide/triamterene and/or memantine, and the pharmacokinetics of memantine was analysed under steady state conditions. AUC, C<sub>max</sub> and T<sub>max</sub> values were within the 80–125% bioequivalence limits compared to values obtained for memantine alone. Similarly, memantine had no significant effect on the kinetics of triamterene or its hydroxymetabolite. However, the rate and extent of hydrochlorothiazide bioavailability was reduced by memantine by about 20%. No clinically relevant impact on the pharmacokinetics of memantine or hydrochlorothiazide/triamterene was observed.

Atropine

Serious interactions between atropine and memantine have been noted in a toxicity study in rats. The interaction with atropine occurred at very high doses of memantine under conditions not relevant to humans treated at therapeutic doses of memantine.

**ADVERSE EFFECTS**

The following table gives an overview of the most frequent (≥ 2% for memantine) adverse events (irrespective of causal relationship) that were observed in the trial population with moderately severe to severe dementia.

<b>System Organ Class &amp; Preferred Term</b>	<b>Placebo n=288 (%)</b>	<b>Memantine n=299 (%)</b>
<b>BODY AS A WHOLE – GENERAL DISORDERS</b>		
Fatigue	3 (1.0)	7 (2.3)
<b>CARDIOVASCULAR DISORDERS - GENERAL</b>		
Oedema peripheral	2 (0.7)	6 (2.0)
<b>CENTRAL &amp; PERIPHERAL NERVOUS SYSTEM DISORDERS</b>		
Dizziness	8 (2.8)	15 (5.0)
Headache	9 (3.1)	15 (5.0)
Confusion	7 (2.4)	9 (3.0)
Gait abnormal	10 (3.5)	8 (2.7)
<b>GASTROINTESTINAL SYSTEM DISORDERS</b>		
Diarrhoea	14 (4.9)	16 (5.4)
Vomiting	6 (2.1)	11 (3.7)
Constipation	13 (4.5)	10 (3.3)
Anorexia	6 (2.1)	9 (3.0)
Faecal incontinence	8 (2.8)	8 (2.7)
Nausea	6 (2.1)	7 (2.3)
<b>LIVER &amp; BILIARY SYSTEM DISORDERS</b>		
Phosphatase alkaline increased	4 (1.4)	6 (2.0)
<b>METABOLIC &amp; NUTRITIONAL DISORDERS</b>		
Hyperglycaemia	5 (1.7)	6 (2.0)
ESR increased	5 (1.7)	8 (2.7)
<b>MUSCULOSKELETAL SYSTEM DISORDERS</b>		
Arthralgia	6 (2.1)	6 (2.0)
Back pain	6 (2.1)	6 (2.0)

System Organ Class & Preferred Term	Placebo n=288 (%)	Memantine n=299 (%)
<b>PSYCHIATRIC DISORDERS</b>		
Agitation	48 (16.7)	26 (8.7)
Insomnia	14 (4.9)	15 (5.0)
Hallucination	6 (2.1)	14 (4.7)
Somnolence	9 (3.1)	10 (3.3)
Anorexia	6 (2.1)	9 (3.0)
Depression	9 (3.1)	8 (2.7)
Anxiety	3 (1.0)	7 (2.3)
Delusion	4 (1.4)	6 (2.0)
Sleep disorder	3 (1.0)	6 (2.0)
<b>RESPIRATORY SYSTEM DISORDERS</b>		
Coughing	16 (5.6)	12 (4.0)
Bronchitis	13 (4.5)	11 (3.7)
Pneumonia	5 (1.7)	7 (2.3)
Upper respiratory tract infection	7 (2.4)	6 (2.0)
<b>SECONDARY TERMS</b>		
Inflicted injury	20 (6.9)	18 (6.0)
Fall	14 (4.9)	14 (4.7)
<b>URINARY SYSTEM DISORDERS</b>		
Urinary incontinence	19 (6.6)	17 (5.7)
Urinary tract infection	22 (7.6)	9 (3.0)
<b>VISION DISORDERS</b>		
Conjunctivitis	1 (0.3)	6 (2.0)

The following adverse events were reported with memantine at a frequency between 1% and < 2% at an incidence greater than placebo in patients with moderately severe to severe AD: pain, abnormal crying, influenza-like symptoms, leg pain, syncope, dependent oedema, hypertonia (increased muscle tone), gastroenteritis, bradycardia, hyperuricaemia, hypertension, dehydration, dyspnoea, hypokalaemia, arthrosis, angina pectoris, purpura, rash, basal cell carcinoma, cerebrovascular disorder, phlebitis, deep thrombophlebitis, tooth ache and tooth caries. As in the above table, causality to memantine has not been established.

Adverse events reported with memantine at a frequency between 1% and 2% that occurred at a similar rate to or less than placebo were: weight decrease, oedema, coma, abdominal pain, cardiac arrest, increased ALT, AST and GGT, diabetes mellitus, aggressive reaction, apnoea, rhinitis, abrasion, micturition frequency and leucocytosis.

#### Treatment – Emergent Adverse Drug Reactions

Although no causal relationship to Memantine treatment has been found, the following adverse events were reported in at least one patient, either from clinical trials or spontaneous reports. All of these events, which are not listed above, either occurred rarely (< 1%) or at an unknown incidence from data originating from spontaneous reports.

Alzheimer's disease has been associated with depression, suicidal ideation and suicide. In post-marketing experience these events have been reported in patients treated with memantine.

#### Body as a Whole – General Disorders

Fever, increased appetite, increased libido, asthenia, somnolence, tiredness.

#### Cardiovascular Disorders

Chest pain, hypotension, postural hypotension, rhythm and rate disturbance (e.g. atrial fibrillation, QTc prolongation, ischaemic event) and sudden death (e.g. myocardial infarction). Cardiac failure- in placebo-controlled clinical trials of memantine an increase in incidence rate has been observed in non-serious cases; no difference was seen in fatal or serious cases. Causal relationship to memantine has not been ascertained.



### **Gastrointestinal System Disorders**

Diverticulitis, dyspepsia, haemorrhoids, gastric ulcer, ileus, pancreatitis.

### **Hepatobiliary Disorders**

Hepatitis, elevated liver function test.

### **Infections and Infestations**

Fungal infections.

### **Metabolic and Nutritional Disorders**

Bilirubinaemia, aggravated diabetes mellitus, hypernatraemia, hyponatraemia.

### **Musculoskeletal Disorders**

Muscle weakness, myalgia, skeletal pain.

### **Neurological Disorders**

Aphasia, speech disorder, hyperkinesia, dyskinesia, dementia, partial epileptic seizure, convulsions, tremor, extrapyramidal disorder, transient ischaemic attack, vertigo, numbness, paraesthesia, mental status changes, balance disorders.

### **Platelet, Bleeding & Clotting Disorders**

Embolism.

### **Psychiatric Disorders**

Delusion, nervousness, stupor, excitation/mania, suicide attempt, psychotic reactions.

### **Renal and Urinary Disorders**

Acute renal failure, abnormal renal function, renal calculus.

### **Reproductive Disorders**

Menstrual disorder.

### **Respiratory System Disorders**

Atelectasis.

### **Red Blood Cell Disorders**

Anaemia.

### **Skin and Appendages Disorders**

Dermatitis, skin disorder, skin ulceration, bullous eruption, pruritus, increased sweating.

### **Urinary System Disorders**

Cystitis, pyuria, haematuria, urinary retention.

### **Vascular (Extracardiac) Disorders**

Cerebrovascular disorder, intracranial haemorrhage, venous thrombosis/thromboembolism (uncommon).

### **Vision Disorders**

Cataract, abnormal vision, glaucoma.

### **Others**

Tooth disorder, inguinal hernia, sepsis.

The following Immune System Disorder Adverse Reaction has been found in clinical studies with memantine and since its introduction in the market, at an incidence classified as common ( $\geq 1/100$  to  $< 1/10$ ):- Drug hypersensitivity.

## **DOSAGE AND ADMINISTRATION**

Memantine tablets should be administered once a day and should be taken at the same time every day with a little liquid, with or without food.

The tolerance and dosing of memantine should be reassessed on a regular basis preferably within three months after start of treatment. Thereafter, the clinical benefit of memantine and the patient's tolerance of treatment should be reassessed on a regular basis according to current clinical guideline. Maintenance treatment can be continued for as long as a therapeutic benefit is favourable and the patient tolerates treatment with memantine. Discontinuation of memantine should be considered when evidence of a therapeutic effect is no longer present or if the patient does not tolerate treatment.

### **Adults**

The recommended maintenance dose is 20 mg per day. This is achieved by upward titration of 5 mg per week. The 10 mg tablet is required for titration as follows:

#### Dose Titration

##### Week 1 (Day 1 - 7)

The patient should take 5 mg ( $\frac{1}{2}$  x 10 mg tablet) per day.

##### Week 2 (Day 8 - 14)

The patient should take 10 mg (1x 10 mg tablet) per day.

##### Week 3 (Day 15 - 21)

The patient should take 15 mg ( $1\frac{1}{2}$  x 10 mg tablets) per day.

### **Maintenance Dose from Week 4**

The recommended maintenance dose is 20 mg per day.

### **Children**

The use of Memantine in children is not recommended.

### **Hepatic Impairment**

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

### **Renal Impairment**

In patients with mildly impaired renal function (creatinine clearance 50–80 mL/min), no dosage adjustment is required.

In patients with moderate renal impairment (creatinine clearance 30–49 mL/min), the daily dose should be 10 mg per day. If tolerated well after at least 7 days of treatment, the dose can be increased up to 20 mg/day according to the standard titration scheme.

In patients with severe renal impairment (creatinine clearance 5–29 mL/min), the daily dose should be 10 mg per day.

## **OVERDOSAGE**

In general, the main therapy for all overdoses is supportive and symptomatic care.

### **Symptoms**

In the event of accidental overdose, no life-threatening clinical signs and symptoms are expected. The toxic effects observed in early single-dose toxicity studies in animals were consistent with acute, high-dose NMDA receptor-blockage and included ataxia, tremor, prone position, bradypnoea, and amnesia.

In one case of suicidal overdose the patient survived the intake of up to 400 mg memantine showing central nervous effects (e.g. restlessness, psychosis, visual hallucinations, proconvulsiveness, somnolence, stupor and unconsciousness) which resolved without permanent sequelae.

### **Treatment**

In the event of overdose, treatment should be symptomatic. Elimination of memantine can be enhanced by acidification of urine.

**For further advice on management of overdose please contact the Poisons Information Centre (Tel: 13 11 26 for Australia).**

### **PRESENTATION AND STORAGE CONDITIONS**

APO-Memantine tablets are intended for oral administration.

#### **APO-Memantine 10 mg Tablets**

White, peanut shaped, biconvex film coated tablet. Engraved “APO” bisect “APO” on one side, “MEM” bisect “10” on the other side.

Blister pack (Clear PVC/PVDC/Aluminium) of 14, 30, 50, 56 & 100 tablets: AUST R 159582.

Bottle (white, round HDPE bottle with white child-resistant cap) of 14, 30, 50, 56 & 1000 tablets: AUST R 159576.

#### **APO-Memantine 20 mg Tablets**

Pale red, oval, biconvex, film coated tablet. Engraved “MEM 20” on one side, “APO” on the other side.

Blister pack (Clear PVC/PVDC/Aluminium or PVC/Aclar film/Aluminium) of 28 tablets: AUST R 207782

Not all strengths, pack types and/or pack sizes may be available.

### **Storage**

Store below 25°C.

### **NAME AND ADDRESS OF THE SPONSOR**

Apotex Pty Ltd  
16 Giffnock Avenue  
Macquarie Park NSW 2113

APO and APOTEX are the registered trade marks of Apotex Inc.

### **POISON SCHEDULE OF THE MEDICINE**

S4 : Prescription Only Medicine.

**Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG) (10 mg) : 29 January 2010**

**Date of most recent amendment (10 mg): 30 June 2012**

**Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG) (20 mg) : 24-Apr-2014**