SAFETY DATA SHEET

Memantine hydrochloride tablets

Strength : 5 mg / 10 mg

Revision No.: 00

Pack Style : Bottle pack of 60,100,500,1000 and blister 10's

EMERGENCY OVERVIEW

Each **Memantine hydrochloride tablets** 5 mg /10 mg intended for oral administration contains 5/10 mg of Memantine Hydrochloride Tablets and excipients generally considered to be non- toxic and non-hazardous in small quantities and under conditions of normal occupational exposure.

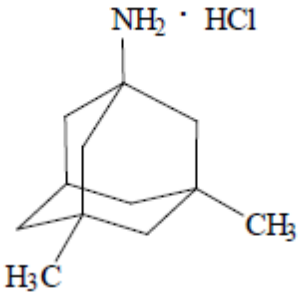
Section 1. IDENTIFICATION OF THE PRODUCT

Product Name: **Memantine hydrochloride tablets**

Active Pharmaceutical Ingredient : **Memantine hydrochloride**

Formula: $C_{12}H_{21}N \cdot HCl$

Chemical Structure:



Mechanism of Action: Memantine is a clinically useful drug in many neurological disorders, including Alzheimer's disease. The principal **mechanism of action** of **memantine** is believed to be the blockade of current flow through channels of N-methyl-d-aspartate (NMDA) receptors--a glutamate receptor subfamily broadly involved in brain function

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Manufacturer / supplier identification

Company:	Cadila Healthcare Ltd. Ahmedabad, India
Address:	Sarkhej – Bavla. N.H. 8A, Moraiya. Tal. Sanand. Dist. Ahmedabad – 382210. State: Gujarat. India
Contact for information:	Tel.: +91 79 6868100 Fax: +91 79 3750319
Emergency Telephone No.	Tel.: +91 79 6868100

Therapeutic Category: To treat moderate to severe Alzheimer's disease.

Indications : Memantine hydrochloride tablets, USP are indicated for the treatment of moderate to severe dementia of the Alzheimer's type

Recommended use: The recommended starting dose of memantine hydrochloride is 5 mg once daily. The dose should be increased in 5 mg increments to 10 mg/day (5 mg twice daily), 15 mg/day (5 mg and 10 mg as separate doses), and 20 mg/day (10 mg twice daily). The minimum recommended interval between dose increases is one week. The dosage shown to be effective in controlled clinical trials is 20 mg/day.

Memantine hydrochloride tablets can be taken with or without food. If a patient misses a single dose of memantine hydrochloride tablets, 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 tablets for several days, dosing may need to be resumed at lower doses and retitrated as described above.

Restriction on Use / Contraindications:

Memantine hydrochloride tablets are contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation.

SECTION 2. HAZARD(S) IDENTIFICATION

Dosage and Administration The recommended starting dose of memantine hydrochloride is 5 mg once daily. The dose should be increased in 5 mg increments to 10 mg/day (5 mg twice daily), 15 mg/day (5 mg and 10 mg as separate doses), and 20 mg/day (10 mg twice daily). The minimum recommended interval between dose increases is one week. The dosage shown to be effective in controlled clinical trials is 20 mg/day.

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Specific Populations

Renal Impairment

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

Hepatic Impairment

Memantine hydrochloride tablets should be administered with caution to patients with severe hepatic impairment

Adverse Effects: Clinical Trials Experience

Memantine hydrochloride was evaluated in eight double-blind placebo-controlled trials involving a total of 1862 dementia (Alzheimer's disease, vascular dementia) patients (940 patients treated with memantine hydrochloride and 922 patients treated with placebo) for a treatment period up to 28 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 clinical practice.

Adverse Events Leading to Discontinuation

In placebo-controlled trials in which dementia patients received doses of memantine hydrochloride up to 20 mg/day, the likelihood of discontinuation because of an adverse reaction was the same in the memantine hydrochloride group (10.1%) as in the placebo group (11.5%). No individual adverse reaction was associated with the discontinuation of treatment in 1% or more of memantine hydrochloride -treated patients and at a rate greater than placebo.

Most Common Adverse Reactions

In double-blind placebo-controlled trials involving dementia patients, the most common adverse reactions (incidence $\geq$ 5% and higher than placebo) in patients treated with memantine hydrochloride were dizziness, headache, confusion and constipation. Table 1 lists all adverse reactions that occurred in at least 2% of patients treated with memantine hydrochloride and at an incidence greater than placebo.

Table 1

Adverse Reactions Reported in Controlled Clinical Trials in at Least 2% of

Patients Receiving memantine hydrochloride and at a Higher Frequency than Placebo-treated Patients.

Adverse Reaction	**Placebo (N = 922) %**	**Memantine (N = 940) %**
Body as a Whole		
Fatigue	1	2
Pain	1	3
Cardiovascular System		
Hypertension	2	4
Central and Peripheral Nervous System		
Dizziness	5	7
Headache	3	6
Gastrointestinal System		
Constipation	3	5
Vomiting	2	3
Musculoskeletal System		
Back pain	2	3
Psychiatric Disorders		
Confusion	5	6
Somnolence	2	3
Hallucination	2	3
Respiratory System		
Coughing	3	4
Dyspnea	1	2

The overall profile of adverse reactions and the incidence rates for individual adverse reactions in the subpopulation of patients with moderate to severe Alzheimer's disease were not different from the profile and incidence rates described above for the overall dementia population.

Seizures

Memantine hydrochloride has not been systematically evaluated in patients with a seizure disorder. In clinical trials of memantine hydrochloride, seizures occurred in 0.2% of patients treated with memantine hydrochloride and 0.5% of patients treated with placebo.

Pregnancy Comments

Warnings & Precautions **Genitourinary Conditions**

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

Section 3. COMPOSITION / INFORMATION ON INGREDIENTS

Component	Exposure limit	CAS no.
Principle component		
memantine hydrochloride	Not found	**41100-52-**1
Inactive ingredients		
colloidal silicon dioxide	Not found	**7631-86-9**
croscarmellose sodium	Not found	74811-65-7
dibasic calcium phosphate	Not found	**7757-93-9 7789-77-**7 (dihydrate)
hypromellose	Not found	**9004-65-**3
microcrystalline cellulose	Not found	9004-34-6
magnesium stearate	Not found	557-04-0
polyethylene glycol	Not found	25322-68-3
povidone	Not found	**9003-39-8**
talc	Not found	**14807-96-**6
titanium dioxide	Not found	**13463-67-7**

Section 4. FIRST -AID MEASURES

Eye Contact No known effect on eye contact, rinse with water for a few minutes.
Skin Contact No known effect on skin contact, rinse with water for a few minutes.
Serious Skin Contact Not available.
Inhalation Allow the victim to rest in a well-ventilated area. Seek immediate medical attention.
Serious Inhalation Not available.
Ingestion Do not induce vomiting. Loosen tight clothing such as a collar, tie, belt or waistband. If the victim is not breathing, perform mouth-to-mouth resuscitation. Seek immediate medical attention..

Section 5. FIRE FIGHTING MEASURES

Specific hazards arising from the chemical:
During fire, gases hazardous to health may be formed.

Special protective equipment and precautions for firefighters:
Self-contained breathing apparatus and full protective clothing must be worn in case of fire
Fire fighting equipment/instructions: Move containers from fire area if you can do so without risk.
Specific methods:
Use standard firefighting procedures and consider the hazards of other involved materials.

General fire hazards: No unusual fire or explosion hazards noted

Fire incompatibility Avoid contamination with oxidizing agents i.e. Nitrates, oxidizing acids, chlorine bleaches, pool chlorine etc. As ignition may result.

Personal protection Glasses
Chemical goggles
Gloves
Respirator
Particulate

Section 6. ACCIDENTAL RELEASE MEASURES

Small Spill: Use appropriate tools to put the spilled solid in a convenient waste disposal container. Finish cleaning by spreading water on the contaminated surface and dispose of according to local and regional authority requirements.

Large Spill: Use a shovel to put the material into a convenient waste disposal container. Finish cleaning by spreading water on the contaminated surface and allow to evacuate through the sanitary system.

Spill Clean Up Procedures Use proper personal protective equipment and clothing. Shut off the source of the spill or leak if it is safe to do so. Scoop or shovel spilled material into a suitable labeled open head drum. Secure the drum cover and move the container to a safe holding area. Wash spill area thoroughly with soapy water.

Treatment and Disposal Decontaminate equipment. Dispose of protective clothing with spilled material.

Environmental precautions Avoid release to the environment. Prevent further leakage or spillage if safe to do so. Avoid discharge into drains, water courses or onto the ground. Inform appropriate managerial or supervisory personnel of all environmental releases.

Section 7. HANDLING AND STORAGE

Storage Store at 20° to 25°C (68° to 77°F). Protect from excessive moisture. Dispense in a tight container

Section 8. EXPOSURE CONTROLS / PERSONAL PROTECTION

Engineering controls	Use process enclosures, local exhaust ventilation, or other engineering controls to keep airborne levels below recommended exposure limits. If user operations generate dust, fume or mist, use ventilation to keep exposure to airborne contaminants below the exposure limit.
Personal Protection	Safety glasses. Labcoat.
Eye/face protection	If contact is likely, safety glasses with side shields are recommended.
Protective Clothing	Protective clothing is not normally necessary, however it is good practice to use apron.
Personal Protection in Case of a Large Spill	Splash goggles. Full suit. Boots. Gloves. Suggested protective clothing might not be sufficient; consult a specialist before handling this product.
Exposure Limit	Data not available

Section 9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance

Physical state	Tablet dosage form
Description	Memantine Hydrochloride Tablets USP, 5 mg are white to off white, capsule shaped, biconvex film coated tablets debossed with 'ZF' on one side and '41' on other side Memantine Hydrochloride Tablets USP, 10 mg are white to off white, capsule shaped, biconvex film coated tablets debossed with 'ZF 40' on one side and other side is plain
Pure/Mixture	Mixture

Section 10. STABILITY AND REACTIVITY

Stability: The product is stable.

Section 11. TOXICOLOGICAL INFORMATION

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 (10 times the maximum recommended human dose [MRHD] on a mg/m^2 basis). There was also no evidence of carcinogenicity in rats orally dosed at up to 40 mg/kg/day for 71 weeks followed by 20 mg/kg/day (20 and 10 times the MRHD on a mg/m^2 basis, respectively) through 128 weeks.

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

No impairment of fertility or reproductive performance was seen in rats administered up to 18 mg/kg/day (9 times the MRHD on a mg/m^2 basis) orally from 14 days prior to mating through gestation and lactation in females, or for 60 days prior to mating in males.

Animal Toxicology and/or Pharmacology

Memantine induced neuronal lesions (vacuolation and necrosis) in the multipolar and pyramidal cells in cortical layers III and IV of the posterior cingulate and retrosplenial neocortices in rats, similar to those which are known to occur in rodents administered other NMDA receptor antagonists. Lesions were seen after a single dose of memantine. In a study in which rats were given daily oral doses of memantine for 14 days, the no-effect dose for neuronal necrosis was 6 times the maximum recommended human dose of 20 mg/day on a mg/m^2 basis.

In acute and repeat-dose neurotoxicity studies 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 levels of the combination were associated with clinically relevant plasma memantine and donepezil exposures.

The relevance of these findings to humans is unknown.

Section 12. ECOLOGICAL INFORMATION

Do not allow product to enter drinking water supplies, waste water or soil.

Ecotoxicity: Not available.

Section 13. DISPOSAL CONSIDERATION

All waste must be handled in accordance with local, state and federal regulations.

Legislation addressing waste disposal requirements may differ by country, state and/ or territory. Each user must refer to laws operating in their area. In some areas, certain wastes must be tracked.
A Hierarchy of Controls seems to be common - the user should investigate:

- Reduction
- Reuse
- Recycling
- Disposal (if all else fails)

This material may be recycled if unused, or if it has not been contaminated so as to make it unsuitable for its intended use. Shelf life considerations should also be applied in making decisions of this type. Note that properties of a material may change in use, and recycling or reuse may not always be appropriate.
DO NOT allow wash water from cleaning equipment to enter drains. Collect all wash water for treatment before disposal.

- Recycle wherever possible.
- Consult manufacturer for recycling options or consult Waste Management Authority for disposal if no suitable treatment or disposal facility can be identified.

Section 14. TRANSPORT INFORMATION

The product is not hazardous when shipping via air (IATA), ground (DOT), or sea (IMDG).

Section 15. REGULATORY INFORMATION

Generic Medicine

Date of issue: February 2, 2019. **Supersedes edition:** New Edition

The information presented in the safety data sheet is, to the best our knowledge, accurate and reliable. It characterizes the product with regard to the appropriate safety precautions. It does not represent a guarantee of the properties of the product,