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# INSTRUCTION
## for medical use

## DENIGMA®

***Composition*:**
*active substance:* memantine;
1 tablet contains 10 mg of memantine hydrochloride;
*excipients:* microcrystalline cellulose, sodium croscarmallose, colloidal anhydrous silicon dioxide, magnesium stearate, Opadry Pink 03F84827 (talc, titanium dioxide (E 171), hypromellose, iron oxide red (E 172), polyethylene glycol).

**Pharmaceutical form.** Coated tablets.
*Basic physical and chemical properties:* oval biconvex pink film-coated tablets with a break line on one side and smooth on the other side.

**Pharmacotherapeutic group.**
Drugs used in dementia. ATC code N06D X01.

***Pharmacological proterties.***
*Pharmacodynamics.*
In the manifestation of symptoms and progression of neurodegenerative dementia significant role is played by glutamatergic neurotransmission violations, especially involving NMDA (N-methyl-D-aspartate) receptors.
Memantine is a voltage-gated, middle affinity noncompetitive NMDA-receptor antagonists. Memantine modulates the effects of pathologically elevated levels of glutamate that may lead to neuronal dysfunction.
*Pharmacokinetics.*
*Absorption.*
Memantine has an absolute bioavailability of approximately 100%; time to reach maximum plasma concentration ($T_{max}$) is between 3 and 8 hours. There is no indication that food influences the absorption of memantine.
*Distribution.*
Daily dose of 20 mg leads to steady-state plasma concentrations of memantine ranging from 70 to 150 ng/ml (0.5-1 μmol) with large interindividual variations. When daily doses of 5 to 30 mg are administered, a mean cerebrospinal fluid (CSF)/serum ratio is 0.52. The volume of distribution is about 10 l/kg. About 45 % of memantine is bound to plasma-proteins.
*Biotransformation.*
In the human body, about 80% of memantine circulates in the form of the initial substance. The main metabolites in humans are N-3,5-dimethyl-gludanthane, an isomeric mixture of 4- and 6-hydroxy-

memantine and 1-nitroso-3,5-dimethyl-adamantane. None of these metabolites have NMDA-antagonistic properties. Participation of cytochrome P450 in in vitro metabolism was not detected.
In a study using 14C-memantine orally, an average of 84% of the dose was excreted within 20 days, with more than 99% excreted by the kidneys.
*Elimination.*
Memantine is eliminated in a monoexponential manner with a terminal $t_{1/2}$ of 60 to 100 hours. In volunteers with normal kidney function, total clearance ($Cl_{tot}$) is 170 ml/min/1.73m$^2$, part of which is due to tubular secretion. The renal stage of the pharmacokinetics of memantine also includes tubular reabsorption, possibly mediated by cationic transport proteins.
The renal elimination rate of memantine under alkaline urine conditions may be reduced by a factor of 7 to 9. Alkalization of urine may result from drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or from the massive ingestion of alkalizing gastric buffers.
*Linearity.*
Pharmacokinetics is linear in the dose range of 10 to 40 mg.
*Pharmacodynamic/ pharmacokinetic relationship.*
At a dose of memantine of 20 mg per day the cerebrospinal fluid levels match the $k_i$-value (inhibition constant) of memantine, which is 0.5 µmol in human frontal cortex.

**Clinical characteristics.**
***Indications.***
Mild to severe Alzheimer's disease.

***Contraindications.***
Hypersensitivity to the active substance or to any of the drug components.

***Interaction with other medicinal products and other forms of interaction.***
Given the pharmacological effect and mechanism of action of memantine, the following interactions are possible.
The mechanism of action suggests that the effects of L-dopa, dopaminergic agonists, and anticholinergics may be enhanced by concomitant treatment with NMDA-antagonists such as memantine. The effects of barbiturates and neuroleptics may be reduced. Concomitant administration of memantine with the antispasmodic agents, dantrolene or baclofen, may modify their effects and a dosage adjustment may be necessary.
Concomitant administration of memantine and amantadine should be avoided because of the risk of pharmacotoxic psychosis. Both compounds are chemically related NMDA-antagonists. The same may be true for ketamine and dextromethorphan (see section "Special warnings and precautions for use"). There are data on the risk of psychosis with the simultaneous use of memantine and phenytoin.
Other medicinal products, such as 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.
Concomitant administration of memantine with hydrochlorothiazide (HCT) or any other combined drug containing HCT, may reduce the serum levels of HCT.
Isolated cases with international normalized ratio (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.
No relevant drug-drug interaction of memantine with glyburide/metformin or donepezil were observed. No influence of memantine on the pharmacokinetics of galantamine was observed.
Memantine does not inhibit CYP 1A2, 2A6, 2C9, 2D6, 2E1, 3A, flavin-containing monooxygenase, epoxide hydrolase or sulphation *in vitro*.

***Special warnings and precautions for use.***
Caution is recommended in patients with epilepsy, history of convulsions or patients with predisposing factors for epilepsy.

Concomitant administration with such N-methyl-D-aspartate (NMDA)-antagonists as amantadine, ketamine or dextromethorphan should be avoided. These compounds affect the same system of receptors as memantine, therefore, adverse effects (mostly related to the central nervous system) may occur more often or be more pronounced (see the section "Interaction with other medicinal products and other types of interactions").
Some factors that may raise urine 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 alkalizing gastric buffers. Also, urine pH may be elevated by states of renal tubulary acidosis (RTA) or severe infections of the urinary tract with *Proteus bacteria*.
There are only limited data on the use of memantine in patients with a recent myocardial infarction, patients with decompensated congestive heart failure (NYHA III-IV), as well as with uncontrolled arterial hypertension, so patients with these diseases should be carefully monitored.

*Use during pregnancy or breast-feeding.*
*Pregnancy*
There are no clinical data while using memantine during pregnancy. Experimental animal studies indicate a potential for reducing intrauterine growth at exposure levels that are identical or slightly higher than at human exposure. The potential risk for humans is unknown. Memantine should not be used during pregnancy unless clearly necessary.
*Breast-feeding*
It is not known whether memantine is excreted in human breast milk but, taking into consideration the lipophilicity of the substance, this probably occurs. Women taking memantine should not breast-feed.
*Fertility*
No adverse effect of memantine on male or female fertility was observed.

*Ability to affect the reactoin rate when driving motor transport or using other mechanisms*
Moderate to severe Alzheimer's disease usually impairs the ability to drive and operate other machinery. At the same time, memantine has a slight or moderate effect on the ability to drive vehicles and operate other mechanisms, therefore ambulatory patients should be especially careful when performing the above operations.

***Dosage and administration.***
Treatment should be initiated and administered under the supervision of a physician experienced in the diagnosis and treatment of dementia in Alzheimer's disease. Therapy should be started only in the presence of a caregiver who will monitor the patient's intake of the drug. The diagnosis is made in accordance with current recommendations. The tolerability and dosage of memantine should be regularly evaluated, preferably within 3 months after initiation of therapy. After that, the clinical benefit of memantine and the patient's tolerability are reassessed on a regular basis in accordance with current clinical recommendations. Maintenance treatment can be continued as long as the therapeutic effect remains favorable and the patient's tolerance of memantine is good. The decision to stop treatment with memantine is considered in the absence of a therapeutic effect or if the patient does not tolerate drug therapy.
Tablets should be taken 1 time a day every day at the same time, regardless of food intake.
*Adults*.
*Dose titration*
The recommended starting dose is 5 mg per day, which should be gradually increased during the first 4 weeks of treatment until the recommended maintenance doses are reached as follows:
1st week (day 1–7): take 5 mg (1/2 tablet) per day during the week;
2nd week (day 8–14): take 10 mg (1 tablet) per day during the week;
3rd week (day 15–21): take 15 mg (1 1/2 tablets) per day during the week;
starting from the 4th week take 20 mg (2 tablets) per day every day.
*Maintenance dose*
The recommended maintenance dose is 20 mg (2 tablets) per day.
*Elderly patients*
The recommended dose for patients over 65 years of age is 20 mg per day (2 tablets) as indicated above.

The duration of treatment is individually determined by a physician experienced in the diagnosis and treatment of Alzheimer's dementia. Tolerability and dosage of metamin should be regularly evaluated better within 3 months from the start of treatment. In future, the clinical effect of metamin and the patient's reaction to the treatment should be evaluated regularly as per the clinical recommendations. Maintenance treatment may be continued until the therapeutic effect remains favorable and the tolerability of memantine remains good. The possibility of discontinuation of treatment with memantine should be considered if signs of therapeutic effect disappear or patient's tolerability of treatment worsens.

*Renal impairment.*

No dose adjustment is required for patients with mild renal impairment (creatinine clearance 50–80 ml/min). Patients with moderate renal impairment (creatinine clearance 30–49 ml/min) should use a daily dose of 10 mg (1 tablet). If this dose is well tolerated by the patient for at least 7 days of treatment, it can be increased to 20 mg (2 tablets) per day according to the standard dose selection scheme. Patients with severe renal dysfunction (creatinine clearance 5–29 ml/min) should be prescribed a daily dose of 10 mg (1 tablet).

*Hepatic impairment.*

No dose adjustment is required for patients with mild or moderate hepatic impairment (Child-Pugh Class A and B). There are no data on the use of memantine in patients with severe hepatic impairment, so it is not recommended to prescribe memantine in patients with severe hepatic impairment.

*Children.*

The drug should not be used by children under the age of 18 due to insufficient data on safety and efficacy.

***Overdose.***

Data on overdose are limited.

*Symptoms*

Relatively large overdoses (200 mg and 105 mg/day for 3 days, respectively) have been associated with either only symptoms of increased fatigability, weakness and/or diarrhea or no symptoms. In the overdose cases below 140 mg or unknown dose the patients revealed symptoms from central nervous system (confusion, apathy, drowsiness, vertigo, agitation, aggression, hallucination, gait disturbance) and/or of gastrointestinal origin (vomiting and diarrhea).

In the most severe known case of memantine overdose (2000 mg), the patient had central nervous system disturbances (the patient was in a coma for 10 days, and later experienced diplopia and agitation). After symptomatic treatment and plasmapheresis, the patient recovered without complications.

In another case of high-dose memantine overdose (400 mg), central nervous system disturbances such as anxiety, psychosis, visual hallucinations, convulsions, drowsiness, stupor, and loss of consciousness were observed. The patient recovered.

*Treatment*

The treatment is symptomatic, there is no specific antidote. Standard clinical procedures to remove active substance material, e.g. gastric lavage, carbo medicinalis (to prevent possible intestinal-hepatic recirculation of memantine), acidification of urine, forced diuresis should be used as appropriate.

In the event of clinical signs or symptoms indicating excessive general stimulation of the central nervous system, symptomatic treatment measures should be used with caution.

***Adverse reactions.***

*Infections and invasions:* fungal infections.

*Immune system disorders:* hypersensitivity.

*Psychiatric disorders:* somnolense, confusion, hallucinations[1], psychotic reactions[2].

*Nervous system disorders:* dizziness, balance disorder, gait disorder, convulsive attacks.

*Cardiac disorders:* cardiac failure.

*Vascular disorders:* arterial hypertension, venous thrombosis/thromboembolism.

*Respiratory system:* dyspnea (shortness of breath).

*Gastrointestinal disorders:* constipation, vomiting, pancreatitis[2].

*Hepatic and gallbladder disorders:* increased liver function tests, hepatitis.

*General disorders:* headache, increased fatigability.

[1]Hallucinations were mainly observed in patients with severe Alzheimer's disease.
[2]Separate messages for medical use.
Alzheimer's disease is associated with depression, suicidal thoughts, and suicide attempts. Such cases have also been reported with memantine.

***Shelf life.*** 3 years.

**Storage conditions.**
Store below 25 °C. Keep out of reach of children.

**Package.**
14 tablets are in a blister, 1 blister is in a carton package. 14 tablets in a blister; 1 blister in a carton package; 10 carton packages in a carton box.

**Conditions of supply.** On prescription.

**Manufacturer.**
KUSUM HEALTHCARE PVT LTD.

**Address.**
SP-289 (A), RIICO Industrial area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan), India.

**Date of last revision.**