APPROVED
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INSTRUCTION
For medical use

DENIGMA®

***Composition*:**
active substance: memantine hydrochloride;
1 ml of solution contains memantine hydrochloride 2 mg;
Exepients: glycerine; Citric Acid monohydrate; metyl parahydroxybenzoate (E 218); propylparahydroxibenzoate (E 216); propylene glycol; Sodium Citrate; Sorbitol (E 420); Flavour "Exotic Fruits"; purified water.

Pharmaceutical form. Oral solution.
Basic physical and chemical properties: colorless, clear solution with a characteristic odor.

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

Pharmacological properties.
Pharmacodynamics.
In the manifestations of symptoms and the progression of neurodegenerative dementia, an important role is played by a violation of glutamatergic neurotransmission, especially with the participation of NMDA (N-methyl-D-aspartate) receptors.
Memantine is a potentially dependent, moderate-affinity uncompetitive NMDA-receptor antagonist. It modulates the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction.
Pharmacocinetics.
Absorption.
After oral administration, memantine is well absorbed. Memantine has an absolute bioavailability of approximately 100%. Mean time to reach maximum plasma concentration (T_{max}) is between 3 to 8 hours. There is no indication that food influences the absorption.
Distribution.
The mean volume of memantine distribution is around 9-11 l/kg. About 45 % of memantine is bound to plasma-proteins.
Biotransformation.
Memantine is subjected to partial hepatic metabolism. The hepatic microsomal enzyme system of CYP450 does not play a significant role in the metabolite of memantine.
Elimination.
Memantine is excreted predominantly in the unaltered form (about 48%) with urine, the half-life in the final phase is 60-80 hours.

The remainder is predominantly converted into three polar metabolites with minimal antagonistic activity of the NMDA receptor: glucuronide conjugate, 6-hydroxymemantine, and 1-nitrosodamined memantine. A total of 74% of the taken dose is excreted as the sum of the main active ingredient and the glucuronide

conjugate. Renal clearance includes active tubular secretion, which is regulated by a pH-dependent tubular reabsorption.

Clinical characteristics.

Indications.

Moderate to severe Alzheimer's disease.

Contraindications.

Hypersensitivity to the active substance or to any other component of the drug.

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 "Administration details").

There are some data of the risk of developing a psychosis with the concomitant use of memantine and phenytoin.

Other substances, 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 blood serum levels of HCT.

Isolated cases with international normalized ratio (INR) increases have been reported in patients when applying memantine who have been 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.

There is no data concerning significant effects of the interaction of memantine with glyburide / metformin or donepezil. No effect 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*.

Administration details.

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

Concomitant use of other 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 reactions (mainly central nervous system related) may be more frequent or more pronounced (see also section "Interaction with other drugs and other forms of interaction").

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 anti-acid stomachic. Also, urine pH level may be elevated by states of renal tubulary acidosis (RTA) or severe infections of the urinary tract caused by *Proteus* bacteria.

Only limited data are available on the use of memantine in patients with recent myocardial infarction, patients with decompensated congestive heart failure (NYHA III-IV), and with uncontrolled arterial hypertension, so careful attention is required in patients with such conditions.

Excipients.
Denigma®, oral solution, 2 mg / ml contains 0.65 g of sorbitol in 1 ml (equivalent to 6.5 g when administered at the recommended maximum daily dose). In the case of certain intolerance to some sugars, consult a physician before taking this medicinal product.
The drug contains methyl parahydroxybenzoate and propyl parahydroxybenzoate, which can cause allergic reactions (possibly delayed).

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.
There was no adverse effect of memantine on the fertility of men and women.

Ability to affect the reactoin rate when driving motor transport or using other mechanisms
Moderate to severe Alzheimer's disease usually causes impairment of driving performance and compromises the ability to use machinery. Furthermore, memantine has minor or moderate influence on driving performance and compromises the ability to use machinery; therefore, outpatients should be warned about the necessity to take special care when carrying out the above-mentioned operations.

Dosage and administration.
Treatment should be initiated and supervised by a physician who has experience in the diagnosis and therapy of dementia in Alzheimer's disease. Therapy should only be started if a caregiver is available who will regularly monitor the intake of the medicinal product by the patient.
Tablets should be administered once a day and should be taken at the same time every day. These tablets can be taken with or without food.

Dosage and administration.
The treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's dementia. Therapy should only be started if a caregiver is available who will regularly monitor the intake of the medicinal product by the patient. Diagnosis should be made according to current guidelines. 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 guidelines. 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.
The drug Denigma®, an oral solution, should be taken once or twice a day, at the same time each day, regardless of food intake. The recommended initial dose of the drug is 5 mg once a day. The dose should be increased by 5 mg weekly (see table 1). The maximum daily dose is 20 mg.

Table 1.

Dosage for adult patients with normal renal function

Type of treatment	*Period*	*Daily dose*	*Dosage frequency*
Dose titration	the 1st week (1-7 day)	5 mg (2,5 ml)	1 time a day
	the 2nd week (8-14 day)	10 mg (5 ml)	2 times a day
	the 3rd week (15-21 day)	15 mg (7,5 ml)	2 times a day
	the 4th weeek (22-28 day)	20 mg (10 ml)	2 times a day
Підтримуюче	The 5th and next weeks of	20 mg (10 ml)	2 times a day

лікування	drug administration		

You can not mix the drug with any other liquid. The oral solution is measured using a special measuring spoon, which comes complete with the preparation.
If a patient misses one dose of Denigma®, it is not necessary to double the dose at the next application. The next dose should be taken according to the schedule of admission. If a patient has missed Denigma® for several days, a dose reduction may be required and then a gradual increase in accordance with the scheme described above.
Renal impairment
In patients with mildly impaired renal function (creatinine clearance is 50 – 80 ml/min) no dose adjustment is required. In patients with moderate renal impairment (creatinine clearance is 30 – 49 ml/min) daily dose should be 10 mg. If tolerated well after at least 7 days of treatment, the dose could be increased up to 20 mg/day according to standard titration scheme. In patients with severe renal impairment (creatinine clearance is 5 – 29 ml/min) daily dose should be 10 mg.
Hepatic impairment.
In patients with mild or moderate hepatic impaired function (A and B classes according Child-Pugh), no dose adjustment is needed. No data on the use of memantine in patients with severe hepatic impairment are available, that's why memantine is not recommended in patients with severe hepatic impairment.

Children.
The drug is not intended for use by children under the age of 18 years.

Overdose
Data on overdose are limited.
Symptoms.
Relative large overdoses (200 mg and 105 mg per day during 3 days, respectively) have been associated with either only symptoms of tiredness, weakness and/or diarrhoea or no symptoms at all. In the overdose cases below 140 mg or unknown dose the patients revealed symptoms from central nervous system (confusion, drowsiness, somnolence, vertigo, agitation, aggression, hallucination and gait disturbance) and/or of gastrointestinal origin (vomiting and diarrhoea).
In the most extreme case of memantine overdose (2000 mg), the patient experienced disturbances from the central nervous system (the patient was in the coma for 10 days, and later there was diplopia and agitation). After symptomatic treatment and plasmapheresis, the patient recovered without consequences.
In another case of a large memantine overdose (400 mg), obsessive disorders of the central nervous system, such as anxiety, psychosis, visual hallucinations, tendency to trial, drowsiness, stupor and loss of consciousness were observed. The patient recovered.
Treatment
Treatment is symptomatic, there is no specific antidote. Standard clinical procedures should be used to remove the active ingredient from the body: gastric lavage, activated charcoal intake (to prevent possible intestinal and hepatic recirculation of memantine), acidification of urine and forced diuresis.
In the case of clinical signs or symptoms indicating excessive general stimulation of the central nervous system, symptomatic treatment should be used with caution.

Adverse reactions.
Blood and lymphatic system disorders: agranulocytosis, leukopenia (as well as neutropenia), pancytopenia, thrombocytopenia, thrombotic thrombocytopenic purpura.
Infections and invasions: fungal infections.
Immune system disorders: hypersensitivity, allergic reactions.
Skin and subcutaneous tissue disorders: skin allergy disorders, including Stevens–Johnson syndrome.
Psychiatric disorders: somnolence, 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 disorders: dyspnea (short breath).
Gastrointestinal disorders: constipation, vomiting, pancreatitis[2].

Hepatobiliary system disorders: increase of parameters of liver function tests, hepatitis.
Renal and urinary track system disorders: acute renal disorder (including the increase of creatinine and renal failure).
General disorders: headache, increased fatigability.
[1]Hallucinations were generally present in the patients with severe Alzheimer's disease.
[2]Individual case reports for medical use.
Alzheimer's disease is associated with depression, suicidal thoughts, suicide attempts. Such cases have also been reported while applying memantine.

Shelf life.
2 years.

Storage conditions.
Store below 25 °C in original package.
Keep out of reach of children.
After the first opening of the bottle, the drug should not be stored for more than 3 months.

Package.
100 ml of solution is in a bottle. Every bottle is in a carton package together with a dosing spoon.

Conditions of supply.
On prescription.

Manufacturer.
KUSUM PHARM LLC.

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