APPROVED
The Order of Ministry of
Health of Ukraine
19.03.2024 № 467
Registration certificate
№ UA/17456/01/01

INSTRUCTION
for medical use

DENIGMA®

Composition:
active substance: memantine hydrochloride;
1 ml of solution contains memantine hydrochloride 2 mg;
excipients: glycerol; citric acid monohydrate; methyl parahydroxybenzoate (E 218); propyl parahydroxybenzote (E 216); propylene glycol; sodium citrate; sorbitol solution (E 420); flavor "Tropical"; purified water.

Pharmaceutical form. Oral solution.
Main physico-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, in particular with the participation of NMDA (N-methyl-D-aspartate) receptors.
Memantine is a voltage-dependent, moderate-affinity noncompetitive NMDA-receptor antagonist. Memantine modulates the effects of a pathologically elevated level of glutamate, which can lead to neuronal dysfunction.

Pharmacokinetics.
Absorption. Memantine is well absorbed following oral administration. Memantine has an absolute bioavailability of approximately 100 %. Mean time to reach the maximum plasma concentration (T_{max}) is between 3 to 8 hours. There is no indication that food affects the absorption.
Distribution. The mean volume of memantine distribution is around 9–11 l/kg. Approximately 45 % of memantine is bound to plasma proteins.
Biotransformation. Memantine undergoes partial hepatic metabolism. The hepatic microsomal CYP450 enzyme system does not play a significant role in the metabolism of memantine.
Elimination. Memantine is excreted predominantly (about 48 %) unchanged in the urine and has a terminal elimination half-life of about 60–80 hours.
The remainder is converted primarily to three polar metabolites which possess minimal NMDA receptor antagonistic activity: the glucuronide conjugate, 6-hydroxy memantine, and 1-nitroso-deaminated memantine. A total of 74 % of the administered dose is excreted as the sum of the parent drug and the glucuronide conjugate. Renal clearance involves active tubular secretion moderated by 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 types of interaction.
Given the pharmacological effect and the 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 dose adjustment may be necessary.
Concomitant use of memantine and amantadine should be avoided due to 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 is data on a possible risk of psychosis with the combination 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 its increased plasma levels.
Co-administration of memantine with hydrochlorothiazide (HCT) or any combination with HCT may result in a possibility of reduced serum levels of HCT.
Isolated cases with international normalized ratio (INR) increases have been reported in patients using memantine who were concomitantly treated with warfarin. Although no causal relationship has been established, close monitoring of prothrombin time or INR is required in patients concomitantly treated with oral anticoagulants and memantine.
There is no data regarding 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 isoenzymes CYP 1A2, 2A6, 2C9, 2D6, 2E1, 3A, flavin-containing monooxygenase, epoxide hydrolase or sulphation *in vitro*.

Administration details.
Caution is recommended when prescribing the drug 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 section "Interaction with other medicinal products and other types 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 alkalizing gastric buffers. Moreover, urine pH level may also be elevated by states of renal tubular acidosis (RTA), or severe infections of the urinary tract caused by *Proteus* bacteria.
Only limited data are available regarding the use of memantine in patients with recent myocardial infarction, decompensated congestive heart failure (NYHA [New York Heart Association] function class III-IV), as well as with uncontrolled hypertension, therefore, patients with these conditions require close supervision.
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 maximum recommended daily dose). In case of established intolerance to some sugars, consult a physician before taking this medicinal product.
The drug contains methyl parahydroxybenzoate and propyl parahydroxybenzoate, which may cause allergic reactions (possibly delayed).

Use during pregnancy or breastfeeding.

Pregnancy. There are no data on the use of memantine during pregnancy. Experimental animal studies indicate a potential for reducing intrauterine growth at exposure levels, which 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.
Breastfeeding. 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 breastfeed.
Fertility. No adverse effects of memantine on male and female fertility were noted.

Effect on reaction rate when driving motor transport or using other mechanisms.
Moderate to severe Alzheimer's disease usually causes impairment of the ability to drive motor transport or use other mechanisms. At that, memantine has minor or moderate influence on the ability to drive motor transport and use other mechanisms, therefore, outpatients should be warned to take special care when performing the above actions.

Dosage and administration.
Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of dementia in Alzheimer's disease. Therapy should be initiated only provided a caregiver is available, who will regularly monitor the administration of the drug by the patient. Diagnosis should be made according to the current guidelines. The tolerability and dosing of memantine should be regularly evaluated, preferably within three months after initiation of therapy. Thereafter, the clinical benefit of memantine and the patient's tolerability of treatment should be regularly re-evaluated according to the current clinical guidelines. Maintenance treatment may be continued for as long as the therapeutic effect is beneficial, and the patient's tolerability of memantine is good. Discontinuation of treatment with memantine is considered in case there is no therapeutic effect or if the patient does not tolerate therapy with the drug.
The medicinal product Denigma®, solution for oral use, should be taken 1 or 2 times per day every day at the same time regardless of food intake. The recommended initial dose of the drug is 5 mg 1 time per day. The dose should be increased in increments of 5 mg weekly (see table). The maximum daily dose is 20 mg.

Table.

Dosage for adult patients with normal renal function

Type of treatment	*Period*	*Daily dose*	*Dosage frequency*
Dose titration	week 1 (day 1–7)	5 mg (2.5 ml)	1 time per day
	week 2 (day 8–14)	10 mg (5 ml)	2 times per day
	week 3 (day 15–21)	15 mg (7.5 ml)	2 times per day
	week 4 (day 22–28)	20 mg (10 ml)	2 times per day
Maintenance treatment	week 5 and following weeks of drug administration	20 mg (10 ml)	2 times per day

The drug should not be mixed with any other liquid. The solution for oral use is measured using a special measuring spoon supplied with the drug.
If a patient misses a single dose of the medicinal product Denigma®, the dose should not be doubled during the next administration. The next dose should be taken according to the administration schedule. If a patient fails to take the medicinal product Denigma® for several days, dose reduction may be required, and thereafter a gradual increase of the dose may be required according to the above-described scheme.
Elderly patients.
The recommended dose for patients over 65 years of age is 20 mg per day (10 ml) as indicated above.
Renal impairment.
In patients with mild renal impairment (creatinine clearance 50–80 ml/min), no dose adjustment is required. In patients with moderate renal impairment (creatinine clearance 30–49 ml/min), the daily dose of 10 mg should be used. If a patient tolerates this dose well for at least 7 days of treatment, the dose may be increased up to 20 mg per day according to the standard titration scheme. In patients with severe renal impairment (creatinine clearance 5–29 ml/min), the daily dose of 10 mg should be prescribed.

Hepatic impairment.
In patients with mild or moderate hepatic impairment (classes A and B according to the Child — Pugh classification), no dose adjustment is required. There are no data on the use of memantine in patients with severe hepatic impairment, therefore it is not recommended to prescribe memantine in patients with severe hepatic impairment.

Children.
The medicinal product is not indicated for use in children under 18 years of age.

Overdose.
Data regarding overdose are limited.
Symptoms.
The use of relatively high doses (200 mg and 105 mg per day for 3 days respectively) has been associated with symptoms, such as fatigue, weakness and/or diarrhea, or complete absence of any symptoms. In cases of overdose with doses below 140 mg or with unknown doses, patients exhibited symptoms associated with central nervous system disorders (confusion, drowsiness, somnolence, vertigo, agitation, aggression, hallucinations, and gait disturbance) and/or gastrointestinal disorders (vomiting and diarrhea).
In the most extreme known case of overdose with memantine (2000 mg), the patient exhibited central nervous system disorders (the patient had been in a coma for 10 days, and thereafter diplopia and agitation were observed). Following symptomatic treatment and plasmapheresis, the patient recovered without sequelae.
In another case of overdose with a high dose of memantine (400 mg), central nervous system disorders, such as restlessness, psychosis, visual hallucinations, susceptibility to cramps, somnolence, stupor and loss of consciousness, were observed. The patient recovered.
Treatment.
Treatment is symptomatic, there is no specific antidote. Standard clinical procedures to eliminate the active substance should be used: gastric lavage, administration of activated charcoal (to prevent the potential entero-hepatic recirculation of memantine), acidification of urine and forced diuresis.
In case of clinical signs or symptoms of general central nervous system overstimulation, symptomatic therapeutic measures should be used with caution.

Adverse reactions.
The frequency of the following adverse reactions is determined as follows: very common — ≥1/10, common — from ≥1/100 to < 1/10, uncommon — from ≥ 1/1000 to < 1/100, rare — from ≥1/10000 to < 1/1000, very rare — < 1/10000, not known — cannot be determined from the available data.
Blood and lymphatic system disorders.
Not known: agranulocytosis, leukopenia (including neutropenia), pancytopenia, thrombocytopenia, thrombotic thrombocytopenic purpura.
Infections and infestations.
Uncommon: fungal infections.
Immune system disorders.
Common: hypersensitivity reactions.
Skin and subcutaneous tissue disorders:
Not known: allergic skin reactions, including Stevens — Johnson syndrome.
Psychiatric disorders.
Common: somnolence.
Uncommon: confusion, hallucinations[1].
Not known: psychotic reactions[2].
Nervous system disorders.
Common: dizziness, balance disorders.
Uncommon: gait abnormal.
Very rare: seizures.
Cardiac disorders.
Uncommon: cardiac failure.

Vascular disorders.
Common: hypertension.
Uncommon: venous thrombosis/thromboembolism.
Respiratory system disorders.
Common: dyspnea (shortness of breath).
Gastrointestinal disorders.
Common: constipation.
Uncommon: vomiting.
Not known: pancreatitis[2].
Hepatobiliary disorders.
Common: elevated liver function tests.
Not known: hepatitis.
Renal and urinary track system disorders:
Not known: acute renal disorder (including the increase of creatinine and renal failure).
General disorders and administration site conditions.
Common: headache.
Uncommon: increased fatigability.
[1] Hallucinations have been mainly observed in patients with severe Alzheimer's disease.
[2] Isolated reports in post-marketing experience.

Alzheimer's disease has been associated with depression, suicidal ideation and suicide. Such cases have also been reported in patients treated with memantine.
Reporting of adverse reactions.
Reporting adverse reactions after the registration of the medicinal product is of great importance. It allows to monitor the correlation of the benefits and risks related to the use of the medicinal product. Healthcare and pharmaceutical professionals, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of efficacy of the medicinal product through the Automated pharmacovigilance information system available at: https://aisf.dec.gov.ua.

Shelf life.
3 years.

Storage conditions.
Store in the original package at a temperature not more than 25 °C.
Keep out of reach of children.
After first opening the bottle, store the drug for no more than 3 months.

Package.
100 ml are in a bottle. Each bottle is in a carton box along with a measuring spoon.

Conditions of supply.
By prescription.

Manufacturer.
LLC "KUSUM PHARM".

Address of manufacturer and manufacturing site.
40020, Ukraine, Sumy region, Sumy, Skryabina Str. 54.

or

Manufacturer.
LLC "GLADPHARM LLC".

Address of manufacturer and manufacturing site.

40020, Ukraine, Sumy region, Sumy, Davydovskoho Hryhoriia Str., 54.

Date of last revision. 12.06.2025