

**PACKAGE LEAFLET**  
**for medical use of a medicinal product**

**Memtec®**

***Qualitative and quantitative composition:***

*active substance:* memantine;

1 oral dispersible tablet contain memantine hydrochloride 10 mg, which is equivalent to 8.31 mg of memantine;

*list of excipients:* polacrillin, sodium hydroxide, purified water<sup>1</sup>, lactose monohydrate, microcrystalline cellulose, mannitol (E 421), sodium croscarmellose, aspartame (E 951), colloidal anhydrous silica, iron oxide red (E 172), mint flavor<sup>2</sup>, magnesium.

<sup>1</sup>most are removed during the process.

<sup>2</sup>mint flavor contains: maltodextrin, modified starch (E 1450), mint oil.

**Pharmaceutical form.** Oral dispersible tablets.

*Main physical and chemical properties:* tablets of light pink color with splashes, round shape with a flat surface, beveled edges and engraved "10" on one side.

**Pharmacotherapeutic group.**

Anti-dementia drugs. Memantine. ATC code N06D X01.

***Pharmacological properties.***

*Pharmacodynamic properties.*

An important role in the manifestation of symptoms and the progression of neurodegenerative dementia is played by impairment of glutamatergic neurotransmission, especially with the participation of NMDA (N-methyl-D-aspartate) receptors.

Memantine is a potential-dependent, medium-affinity non-competitive NMDA receptor antagonist. Memantine modulates the effects of pathologically elevated levels of glutamate, which can lead to neuronal dysfunction.

*Pharmacokinetic properties.*

*Absorption:* The absolute bioavailability of memantine is approximately 100%, the time to peak plasma concentration ( $T_{max}$ ) - from 3 to 8 hours.

There are no signs of the influence of food on absorption.

*Distribution.* The daily dose of 20 mg causes a stable concentration of memantine in blood plasma in the range from 70 to 150 ng/ml (0.5-1  $\mu$ mol) with significant individual variations. When using daily doses from 5 to 30 mg, the ratio of the content of the medicinal product in the cerebrospinal fluid and serum is equal to 0.52. Approximately 45% of memantine is bound to plasma proteins.

*Biotransformation.* In the human body, about 80% of memantine circulates as a starting substance, the main metabolites do not have NMDA-antagonistic properties. The involvement of cytochrome P450 in *in vitro* metabolism has not been identified.

***Elimination.*** Memantine is eliminated monoexponentially with an interval of  $T_{1/2}$  from 60 to 100 hours. In volunteers with normal renal function, the total clearance ( $Cl_{tot}$ ) was 170 ml / min / 1.73 m<sup>2</sup>. The renal stage of memantine pharmacokinetic properties also includes tubular reabsorption. The rate of renal elimination of memantine under conditions of an alkaline urine reaction can be reduced by 7-9 times. Urinary alkalization can occur as a result of significant dietary changes, such as replacing a rich meat-based diet with a vegetarian one, or as a result of intensive intake of gastric antacids.

***Linearity.*** Pharmacokinetic properties are linear in the dose range of 10-40 mg.

***Pharmacodynamic properties/ pharmacokinetic properties relationship.*** At a dose of 20 mg memantine per day, the level of content in the cerebrospinal fluid corresponds to the value of  $k_i$  (inhibition constant) of memantine, which is 0.5  $\mu$ mol in the area of the human frontal cortex.

### **Clinical particulars.**

#### ***Therapeutic indications.***

Mild to severe Alzheimer's disease.

#### ***Contraindications.***

Hypersensitivity to the active substance or to any component of the medicinal product.

#### ***Interaction with other medicinal products and other forms of interaction.***

The mechanism of action suggests a possible enhancement of the effects of L-dopa, dopaminergic agonists and anticholinergic medicinal products with the simultaneous use of NMDA antagonists such as memantine. It is possible to weaken the effects of barbiturates and antipsychotics.

Concomitant use of memantine and amantadine should be avoided due to the risk of pharmacotoxic psychosis. Both compounds are chemically bound NMDA antagonists. The same can be said about ketamine and dextromethorphan. One of the published reports also noted the possible risk of a combination of memantine and phenytoin.

Other medicinal products, such as cimetidine, ranitidine, procainamide, quinidine, quinine and nicotine, which use the same cationic renal transport system as amantadine, may also be able to interact with memantine, posing a potential risk of increased memantine levels in plasma.

Co-administration of memantine with hydrochlorothiazide (HCT) or any combination of HCT may decrease serum HCT levels.

There have been isolated reports of an increase in the international normalized ratio (INR) with the use of memantine in patients taking warfarin. Although no causal relationship has been established, careful monitoring of prothrombin time or INR is required in patients taking oral anticoagulants concomitantly.

In the course of pharmacokinetic properties studies with the participation of healthy volunteers, no significant effects of the interaction of memantine with glyburide / metformin, donepezil or galantamine were found.

Memantine *in vitro* is not an inhibitor of CYP 1A2, 2A6, 2C9, 2D6, 2E1, 3A, flavin-containing monooxygenase, epoxide hydrolase or sulfation.

#### ***Special warnings and precautions for use.***

Care should be taken when prescribing the drug to patients with epilepsy, patients with a history of seizure episodes, as well as patients with risk factors for the development of epilepsy.

Concomitant use of the medicinal product with N-methyl-D-aspartate (NMDA) antagonists such as amantadine, ketamine or dextromethorphan should be avoided. These compounds affect the same receptor system as memantine, so side effects (mostly related to the central nervous system) may be more frequent or more severe. Several factors that cause an increase in urine pH may necessitate close monitoring of the patient. These factors include significant dietary changes, such as replacing a rich meat-based with a vegetarian diet, or intensive intake of gastric antacids. In addition, urine pH may rise due to a condition of renal tubular acidosis (TRA) or severe urinary tract infections caused by *Proteus bacteria*.

Patients with recent myocardial infarction and patients with decompensated congestive heart failure (III-IV degree), as well as with uncontrolled arterial hypertension were not included in the number of study participants, so there are only limited data on them. Patients with such diseases need close supervision.

*Important information about excipients.*

The medicinal product contains lactose, so it should not be prescribed to patients with rare hereditary forms of galactose intolerance, lactase deficiency or glucose-galactose malabsorption syndrome.

*Fertility, pregnancy and lactation.*

There are no clinical data on the effects of memantine when used during pregnancy. Experimental studies in animals indicate the possibility of retardation of fetal growth when exposed to concentrations identical to or slightly higher than those used in humans. The potential risk for humans is unknown. Memantine should not be used during pregnancy, except in cases specified by a clear and obvious need.

It is not known whether memantine is excreted into breast milk, however, it may occur, given the lyophilicity and lyophobicity of the substance. Women who use memantine should refrain from breastfeeding.

*Effects on ability to drive and use machines.*

Moderate to severe Alzheimer's disease usually impairs the ability to drive and operate machinery. In addition, memantine has little or moderate effect on the rate of human response, so outpatients should be warned to take extra care when driving or operating equipment.

*Posology and method of administration.*

Treatment should be initiated and performed under the supervision of a physician. Therapy should be initiated only in the presence of a guardian who will regularly monitor the patient's intake of the medicinal product.

The tablets should be taken once a day every day at the same time. The tablets can be taken with or without food.

*Adults.*

The maximum daily dose is 20 mg. In order to reduce the risk of adverse reactions, the maintenance dose is determined by gradually increasing the dose by 5 mg per week for the first 3 weeks as follows:

1st week (1–7th day): take 5 mg per day for a week;

2nd week (8–14th day): take 10 mg per day for a week;

3rd week (15–21th day): take 15 mg per day for a week;

starting from the 4th week: take 2 tablets (20 mg per day) every day.

The recommended maintenance dose is 20 mg per day.

The duration of treatment is individually determined by the physician, who must have experience in diagnosing and treating Alzheimer's disease. The tolerance and dosage of memantine should be regularly assessed, especially in the first 3 months of treatment. Subsequently, the clinical effect of memantine and the patient's response to treatment should be evaluated regularly in accordance with current clinical guidelines. Maintenance treatment can be continued as long as the therapeutic effect remains favorable and the tolerability of memantine is good.

Consideration should be given to discontinuing treatment with memantine if signs of a therapeutic effect disappear or if treatment tolerance worsens.

*Elderly patients.*

Based on the results of clinical studies, the recommended dose for patients over 65 years of age is 20 mg per day (2 tablets of 10 mg once daily), as described above. *Decreased renal function.*

For patients with impaired renal function of mild severity (creatinine clearance 50–80 ml/min), a decrease in the dose of the medicinal product is not required. In patients with moderate renal impairment (creatinine clearance 30–49 ml/min), the daily dose should be reduced to 10 mg. The dose can be increased to 20 mg per day according to the standard scheme, if there are no adverse reactions

after at least 7 days of treatment. In patients with severe renal impairment (creatinine clearance 5–29 ml / min), the daily dose should be reduced to 10 mg.

*Decreased liver function.*

No dose adjustment is required for patients with mild to moderate hepatic impairment (Child Pugh A, B). The use of memantine in patients with severe hepatic impairment is not recommended.

*Children.*

The medicinal product is not used in children due to insufficient data on safety and efficacy of its use.

***Overdose.***

Experience is limited.

*Symptoms.*

Relatively significant overdoses (200 mg and 105 mg daily for 3 days, respectively) were either associated with symptoms such as fatigue, weakness, and/or diarrhea, or were asymptomatic. In case of an overdose with a dose of up to 140 mg or an unknown dose, symptoms of central nervous system disorders (confusion, lethargy, drowsiness, dizziness, agitation, aggression, hallucinations, gait disturbances) and/or gastrointestinal disturbances (vomiting and diarrhea) were observed.

after taking 2000 mg of memantine, the patient developed a coma that lasted 10 days, later - diplopia and activation. After symptomatic treatment and plasmapheresis, the patient recovered without adverse effects.

*Treatment*

Symptomatic, specific antidote does not exist. Standard clinical procedures should be used to remove the active substance from the body, such as gastric lavage, administration of activated charcoal, acidification of the urine reaction, forced diuresis.

In case of overstimulation of the central nervous system, symptomatic treatment measures should be used with caution.

***Undesirable effects.***

According to the available data, it is known that in clinical studies of memantine, the overall incidence of adverse events did not differ from that of placebo, and the adverse events were usually mild to moderate in severity.

Adverse events have been ranked under headings of frequency using the following convention: Very common ( $\geq 1/10$ ); common ( $\geq 1/100$ ,  $< 1/10$ ); uncommon ( $\geq 1/1000$ ,  $< 1/100$ ); rare ( $\geq 1/10000$ ,  $< 1/1000$ ); very rare ( $< 1/10000$ ); frequency unknown (cannot be estimated from the available data).

System, organ, class	Frequency	Undesirable effects.
<i>Infections and invasions</i>	Uncommon	Fungal diseases
<i>Immune system disorders</i>	Common	Hypersensitivity
<i>Psychiatric disorders:</i>	Common	Somnolence
	Uncommon	Confusion of consciousness
	Uncommon	Hallucinations <sup>1</sup>
	Frequency unknown	Psychotic reactions <sup>2</sup>
<i>Nervous system disorders</i>	Common	Dizziness
	Common	Balance disorders
	Uncommon	Gait disorders
	Very rare	Seizures
<i>Cardiac disorders</i>	Uncommon	Heart failure
<i>Vascular disorders:</i>	Common	Arterial hypertension.
	Uncommon	Venous thrombosis / thromboembolism
<i>Respiratory, thoracic and mediastinal disorders</i>	Common	shortness of breath
<i>Gastrointestinal disorders</i>	Common	Constipation

	Uncommon	Vomiting
	Frequency unknown	Pancreatitis <sup>2</sup>
<i>Hepatobiliary disorders</i>	Common	Increased liver function
	Frequency unknown	Hepatitis
<i>General disorders and administration site conditions:</i>	Common	Headache
	Uncommon	Increased fatigability

<sup>1</sup>Hallucinations were mainly observed in patients with severe Alzheimer's disease.

<sup>2</sup>Separate reports for medical use

Alzheimer's disease is associated with depression, suicidal ideation and suicide. Such cases are known in the medical use of memantine.

#### Reported suspected adverse reactions.

Reporting suspected adverse reactions after registration of a medicinal product is an important procedure. This allows for continued monitoring of the benefit/risk ratio for the respective drug. Healthcare providers should be informed of any suspected adverse reactions through the national alert system.

**Shelf life.** 3 years.

#### **Special precautions for storage.**

Store in the original package at a temperature below 25°C.

Keep out of the reach of children.

**Nature and contents of container.** 15 tablets in a blister, 2 blisters in a carton pack.

**Category of release.** Prescription only medicine.

**Marketing authorisation holder.** PrJSC “Pharmaceutical firm “Darnitsa”.

**The marketing authorisation holder's location and address of the place of business.**

13, Boryspilska Street, Kyiv, 02093, Ukraine.

**Manufacturer.** Genepharm S.A.

**The manufacturer's location and address of the place of business.**

18km Marathon Avenue, Pallini Attici, 15351, Greece.

**Date of last revision.**