

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PHOCUSS® 10 mg/20 mg film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

Donepezil hydrochloride 10.00 mg (equivalent to 9.12 mg donepezil)

Memantine hydrochloride 20.00 mg (equivalent to 16.62 mg memantine)

Excipients:

Lactose monohydrate (bovine source) 250.00 mg

For excipients see 6.1.

1. PHARMACEUTICAL FORM

Film coated tablet

Pink, scored, oblong film-coated tablets

The purpose of the notch is to make it easier to break the film-coated tablet for swallowing, the film-coated tablet can be divided into equal halves.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indications

PHOCUSS® is indicated for the symptomatic treatment of moderate to severe Alzheimer's type dementia.

2.2 Posology and method of administration

Posology / Frequency and duration of administration:

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's disease.

PHOCUSS® is used for the maintenance treatment of Alzheimer's patients treated with 10 mg donepezil per day, when additional memantine is needed, and in patients suitable for combination therapy of 10 mg donepezil + 20 mg memantine per day.

The dose of memantine should be increased gradually according to the titration scheme below.

Adults:

Dose titration;

Week 1 (days 1-7):

The patient should take one 10 mg/5 mg film-coated tablet once daily for 7 days.

Week 2 (days 8-14):

The patient should take one 10 mg/10 mg film-coated tablet once daily for 7 days.

Week 3 (days 15-21):

The patient should take one 10 mg/15 mg film-coated tablet once daily for 7 days.

Week 4 (days 21-28):

The patient should take one 10 mg/20 mg film-coated tablet once daily for 7 days.

Another pharmaceutical dosage form, the product named PHOCUSS Treatment Start Package, easily allows dose titration of memantine in patients suitable for donepezil + memantine combination therapy.

Maintenance:

The patient should take one PHOCUSS® 10 mg/20 mg film-coated tablet once daily.

Application Method:

PHOCUSS® used orally

Unless directed otherwise by your doctor, the recommended dose for PHOCUSS® is one film-coated tablet taken each night at bedtime.

Additional information regarding special populations:

Kidney Failure:

There is no need to adjust the dose of donepezil in patients with renal failure. No dosage adjustment of memantine hydrochloride is required in patients with mild renal impairment (creatinine clearance 50-80 ml/min). In patients with moderate renal impairment (creatinine clearance 30-49 ml/min), the daily dose of memantine hydrochloride should be 10 mg. If well tolerated after 7 days of treatment, the daily dose can be increased to 20 mg according to the standard titration scheme. For patients with severe renal impairment (creatinine clearance 5-29 ml/min), the daily dose of memantine hydrochloride should be 10 mg.

Liver Failure:

In mild to moderate hepatic impairment, the dose of donepezil should be increased gradually according to the patient's tolerance due to the possibility of longer exposure to the drug. As a result of studies conducted with 10 patients with stable alcoholic cirrhosis, it was observed that donepezil hydrochloride clearance decreased by 20%. There are no data on the use of donepezil hydrochloride in patients with severe hepatic impairment.

No dose adjustment of memantine hydrochloride is required in patients with mild or moderate hepatic impairment (Child-Pugh A and Child-Pugh B). There are no data on the use of memantine hydrochloride in patients with severe hepatic impairment. The use of memantine hydrochloride is not recommended in patients with severe hepatic impairment.

Pediatric population:

The safety and effectiveness of PHOCUSS® in children and adolescents have not been established. Therefore, it is not recommended for use in children under 18 years of age.

Geriatric population:

PHOCUSS® can be used in the geriatric population at the doses indicated above.

2.2 Contraindications

It is contraindicated in patients with hypersensitivity to memantine hydrochloride, donepezil hydrochloride, piperidine derivatives or any of the ingredients of PHOCUSS®.

2.3 Special usage warnings and precautions**Donepezil hydrochloride**

The use of donepezil has not been studied in patients with severe Alzheimer's type dementia, patients with other types of dementia, or patients with other types of memory impairment (e.g., age-related cognitive decline).

Anesthesia: Donepezil, a cholinesterase inhibitor, may increase succinylcholine-type muscle relaxation during anesthesia.

Cardiovascular Conditions: Due to their pharmacological effects, cholinesterase inhibitors may have vagotonic effects on heart rate (such as bradycardia). The potential for this effect may be particularly important in patients with other supraventricular cardiac conduction conditions such as “sick sinus syndrome,” sinoatrial, or atrioventricular block. There have been reports of syncope and convulsions. Heart block or prolonged sinus pause should be considered when examining these patients.

Gastrointestinal Conditions: Patients at high risk of developing ulcers, such as those with a history of ulcers or those taking concomitant nonsteroidal anti-inflammatory drugs (NSAIDs), should be closely monitored for symptoms. However, clinical studies comparing donepezil with placebo showed no increase in the incidence of peptic ulcers or gastrointestinal bleeding.

Genitourinary System: Although not observed in Donepezil clinical studies, cholinomimetics may cause bladder outlet obstruction.

Neurological Conditions: Seizures: Cholinomimetics are believed to have the potential to cause generalized convulsions. However, seizures can also be a sign of Alzheimer's disease. Cholinomimetics have the potential to induce or increase extrapyramidal symptoms.

Neuroleptic Malignant Syndrome (NMS): NMS is a life-threatening disease and is characterized by hyperthermia, muscle rigidity, autonomic instability, altered state of consciousness, and increased serum creatine phosphokinase levels; In addition, myoglobinuria (rhabdomyolysis) and acute renal failure may also occur. NMS due to donepezil use has been reported rarely, especially in patients using concomitant antipsychotics. If the patient has

symptoms indicating NMS or has an unexplained high fever in the absence of other clinical signs of NMS, donepezil treatment should be discontinued.

Pulmonary Conditions: Due to their cholinomimetic effects, cholinesterase inhibitors should be used with caution in patients with a history of asthma or obstructive pulmonary disease. Concomitant use of donepezil with other acetylcholinesterase inhibitors, cholinergic agonists or antagonists should be avoided.

Severe hepatic impairment: No data are available in patients with severe hepatic impairment.

Mortality in vascular dementia clinical trials: Three 6-month clinical studies were conducted examining individuals who met NINDS-AIREN criteria for likely or probable vascular dementia (VaD). NINDS-AIREN criteria define dementia as arising from purely vascular causes.

It was designed to identify patients and exclude patients with Alzheimer's disease from the study. Mortality rates in the first study were 2/198 (1.0%) for 5 mg donepezil hydrochloride, 5/206 (2.4%) for 10 mg donepezil hydrochloride, and 7/199 (3.5%) for placebo. Mortality rates in the second study were 4/208 (1.9%) for 5 mg donepezil hydrochloride, 3/215 (1.4%) for 10 mg donepezil hydrochloride, and 1/193 (0.5%) for placebo. Mortality rates in the third study were 11/648 (1.7%) for 5 mg donepezil hydrochloride and 0/326 (0%) for placebo.

When the mortality rate data from these three VaD studies are combined, the mortality rate in the donepezil hydrochloride group (1.7%) is numerically higher than the mortality rate in the placebo group (1.1%). However, this result was not found to be statistically significant.

Mortality in patients using donepezil hydrochloride or placebo was determined to have various vascular causes, which is an expected result for the elderly population with underlying vascular diseases.

Analysis of fatal and non-fatal vascular events showed no difference in incidence in the donepezil hydrochloride group compared to placebo.

When the Alzheimer's disease studies were combined (n=4146) and these studies were combined with other dementia studies including vascular dementia (n=6888), the mortality rate in the placebo group numerically exceeded the mortality rate in the donepezil hydrochloride group.

Memantine hydrochloride

Caution should be exercised when used in patients with epilepsy, a history of convulsions, or a tendency to epilepsy.

Amantadine should not be used together with NMDA (N-methyl-D-aspartate) antagonists such as dextromethorphan and ketamine. These compounds act on the same receptor system as memantine

hydrochloride and may cause adverse effects (especially those related to the central nervous system) to occur more frequently or to be more severe (see 4.5 Interactions with other medicinal products and other forms of interaction).

If there are factors that increase urine pH (see 5.2 Pharmacokinetic properties - Elimination), careful monitoring of the patient may be required. These factors include a radical change in diet (such as a switch from a carnivore to a vegetarian diet) or the ingestion of large amounts of alkalinising gastric buffers. Urine pH may also be elevated by renal tubular acidosis (RTA) or serious urinary tract infections caused by *Proteus* bacteria.

In many clinical studies, recent myocardial infarction, uncompensated congestive heart failure (New York Heart Association (NYHA) index III-IV), or uncontrolled heart failure Non-hypertensive patients were excluded from the study. Consequently, patients with this condition should be kept under close observation as limited data are available.

PHOCUSS® contains bovine lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not use this medicine.

2.2 Interactions with other medicinal products and other forms of interaction

Donepezil hydrochloride

Donepezil hydrochloride and/or any of its metabolites do not inhibit the metabolism of theophylline, warfarin, cimetidine or digoxin in humans. The metabolism of donepezil hydrochloride is not affected by concurrent use with digoxin or cimetidine.

In vitro studies have shown that cytochrome P450 isoenzyme CYP3A4 and, to a lesser extent, isoenzyme CYP2D6 are involved in donepezil metabolism. In vitro drug interaction studies indicate that ketoconazole, a CYP3A4 inhibitor, and quinidine, a CYP2D6 inhibitor, inhibit the metabolism of donepezil. Therefore, this and other CYP3A4 inhibitors (such as itraconazole and erythromycin) and CYP2D6 inhibitors (such as fluoxetine) may inhibit the metabolism of donepezil. In a study in healthy volunteers, ketoconazole increased mean donepezil concentrations by 30%.

Enzyme inducers such as rifampicin, phenytoin, carbamazepine, and alcohol may decrease donepezil levels. Since the level of inhibitory or inducing effect is unknown, such drug combinations should be used with caution. Donepezil has the potential to interact with drugs that have anticholinergic activity. There is also the potential for synergistic activity with concomitant treatments with drugs such as succinicholine, other neuromuscular blocking agents, or cholinergic agonists or beta-blocking agents that have effects on cardiac conduction.

Memantine hydrochloride

Due to the pharmacological effects and other mechanisms of action of memantine hydrochloride, the following interactions may occur:

- Due to the mode of action of memantine; The effects of L-dopa, dopaminergic agonists, and anticholinergics may be enhanced when used with NMDA antagonists such as memantine. It may reduce the effects of barbiturates and neuroleptics. Concomitant use of memantine with antispasmodic agents, dantrolene or baclofen; may modify its effects and require dosage adjustment.
- Concomitant use of memantine with amantadine should be avoided due to the risk of pharmacotoxic psychosis. Both substances are NMDA-antagonists. The same approach applies to ketamine and may also apply to dextromethorphan (see Section 4.4 Special warnings and precautions for use). There is one published case report regarding the possible risk of combined use of memantine and phenytoin.
- Cimetidine, ranitidine, procainamide, quinidine, quinine and nicotine, which use the same renal cationic transport system as amantadine, may also possibly interact with memantine and pose a risk of increased plasma levels.
- If memantine is used with hydrochlorothiazide (HCT) or any combination with HCT, a decrease in the serum level of HCT is possible.
- In post-marketing experience, isolated cases of increased INR (International normalized ratio) have been reported in patients using memantine concomitantly with warfarin. Although a causal relationship has not been established, close monitoring of prothrombin time or INR is recommended for patients treated concomitantly with oral anticoagulants.

No significant drug interactions were observed between memantine and the glyburide/metformin combination or donepezil in single-dose pharmacokinetic studies in healthy young volunteers.

In a clinical study in healthy young volunteers, no significant effect of memantine on galantamine pharmacokinetics was observed.

Memantine; It did not inhibit CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A, flavin-containing monooxygenase, epoxide hydrolase, or sulfation in vitro.

Additional information regarding special populations

No interaction studies in special populations were identified.

Pediatric population:

No interaction studies in special populations were identified.

2.2 Pregnancy and lactation

General advice

Pregnancy category C.

Women of childbearing potential/Birth control (Contraception):

There is no sufficient data on the use of PHOCUSS® in pregnant women.

There is no recommendation for the use of the drug in women of childbearing potential and those using birth control (contraception).

Pregnancy period

There is no sufficient data on the use of donepezil during pregnancy. Animal studies have not shown teratogenic effects, but perinatal and postnatal toxicity has been observed. The potential risk to humans is unknown.

There are no or limited data on the use of memantine in pregnancy. Animal studies indicate that memantine produces reduced intrauterine growth at exposure levels equal to or slightly higher than in humans. The potential risk to humans is unknown.

PHOCUSS® should not be used during pregnancy unless absolutely necessary.

Lactation period

Although donepezil is excreted in breast milk in rats, there is no information on whether the drug is excreted in human milk.

There is no information regarding the excretion of memantine into human milk; however, this is likely due to the lipophilicity of the substance. PHOCUSS® should not be used in breastfeeding mothers.

Reproductive ability/Fertility

Donepezil hydrochloride had no effect on fertility in rats.

No adverse effects of memantine on male and female fertility have been reported.

2.2 Effects on ability to drive and use machines

Alzheimer's type dementia may cause impairment in driving performance or reduce the ability to operate machinery. In addition, PHOCUSS® may cause weakness, dizziness and muscle cramps, especially when starting or increasing the dose. The ability of Alzheimer's patients who receive PHOCUSS® treatment and continue to drive and use machines should be evaluated regularly by the physician administering the treatment. PHOCUSS® may slightly or moderately impair the ability to drive or use machines.

2.3 Undesirable effects

Adverse drug reactions are listed below by defined frequency:

Very common ($\geq 1/10$);

common ($\geq 1/100$ to $< 1/10$),

uncommon ($\geq 1/1,000$ to $< 1/100$);

rare ($\geq 1/10,000$ to $< 1/1,000$);

very rare ($< 1/10,000$),

not known (cannot be estimated from the available data).

Donepezil hydrochloride

The most common undesirable effects are diarrhea, muscle cramps, fatigue, nausea, vomiting and insomnia.

Infections and infestations

Common: Common cold

Metabolism and nutritional diseases

Common: Anorexia

Psychiatric diseases

Common: Hallucinations**, agitation**, aggressive behavior**, abnormal dreams and nightmares**

Nervous system diseases

Common: Syncope*, dizziness, insomnia Uncommon: Seizure*

Rare: Extrapyramidal symptoms Very rare: Neuroleptic malignant syndrome

Cardiac diseases

Uncommon: Bradycardia

Rare: Sinoatrial block, atrioventricular block

Gastrointestinal diseases

Very common: Diarrhea, nausea

Common: Vomiting, abdominal discomfort

Uncommon: Gastrointestinal bleeding, gastric and duodenal ulcers, increased salivation.

Hepatobiliary diseases

Rare: Liver dysfunction including hepatitis***

Skin and subcutaneous tissue diseases

Common: Rash, itching

Musculoskeletal disorders, connective tissue and bone diseases

Common: Muscle cramps, rhabdomyolysis*****

Kidney and urinary tract diseases

Common: Urinary incontinence

General disorders and diseases related to the application site

Very common: Headache

Common: Fatigue, pain

Studies

Uncommon: Mild elevations in serum muscle creatine kinase concentrations.

Injury and poisoning

Common: Accident

* The possibility of heart block or long pauses in sinus rhythm should be considered when examining patients for syncope or seizure (see section 4.4).

** Reports of hallucinations, abnormal dreams, nightmares, agitation, and aggressive behavior were resolved by reducing the dose or discontinuing treatment.

*** In case of unexplained liver dysfunction, discontinuation of PHOCUSS® should be considered.

**** The possibility of a close temporal relationship with the beginning of donepezil treatment or dose increase, independent of Rhabdomyolysis, Neuroleptic Malignant Syndrome, should be considered.

Memantine hydrochloride

In clinical trials in mild, moderate and severe dementia, including 1784 memantine-treated patients and 1595 placebo-treated patients, the overall incidence rate of adverse events with memantine did not differ from that seen with placebo; Adverse events are generally mild to moderate in intensity. The most frequently occurring adverse events with a higher incidence in the memantine group than in the placebo group were: dizziness (6.3%-5.6%, respectively), headache (5.2%-3.9%), constipation (4.6%-5.6%, respectively), somnolence (3.4%-2.2%) and hypertension (4.1%-2.8%).

Infections and infestations

Uncommon: Fungal infections

Immune system diseases

Common: Hypersensitivity

Psychiatric diseases

Common: Somnolence

Uncommon: Confusion, hallucinations¹ Not known: Psychotic reactions²

Nervous system diseases

Common: Dizziness, balance disorders Uncommon: Gait abnormality

Very rare: Seizures

Cardiac diseases

Uncommon: Heart failure

Vascular diseases

Common: Hypertension

Uncommon: Venous thrombosis/thromboembolism

Respiratory, thoracic disorders and mediastinal diseases

Common: Dyspnea

Gastrointestinal disorders

Common: Constipation

Uncommon: Vomiting

Not known: Pancreatitis²

Hepatobiliary diseases

Common: Increased liver function test

Unknown: Hepatitis

General disorders and diseases related to the application site

Common: Headache

Uncommon: Fatigue

1 Hallucinations have been observed mostly in patients with severe Alzheimer's disease.

2 Isolated cases reported from post-marketing experience.

It has been associated with Alzheimer's disease, depression, suicidal ideation, and suicide. These events have been reported in patients treated with memantine in post-marketing experience.

Reporting of Side Effects:

Talk to your doctor, pharmacist or nurse if you experience any side effects listed or not listed in this leaflet. Also reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

2.2 Overdose and treatment

Donepezil hydrochloride

The expected mean lethal dose of donepezil hydrochloride administered as a single oral dose in mice and rats is 45 and 32 mg/kg, respectively, which are approximately 225 and 160 times the maximum recommended human dose of 10 mg, respectively. Dose-related signs of cholinergic stimulation have been observed in animals and include decreased agitation, prone position, staggering when walking, lacrimation, clonic convulsions, respiratory distress, salivation, miosis, fasciculation, and decreased body surface temperature.

Overdosage with cholinesterase inhibitors may result in cholinergic crisis, characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory distress, collapse, and convulsions. Increased muscle weakness is a possibility and may result in death if respiratory muscles are involved.

As in every case of overdose, general support measures should be used. In case of overdose of donepezil hydrochloride, tertiary anticholinergics such as atropine can be used as an antidote. Intravenous administration of atropine sulfate titrated to effect is recommended: an initial intravenous dose of 1 to 2 mg may be followed by subsequent doses depending on clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when taken concomitantly with quaternary anticholinergics such as glycopyrrolate. It is not known whether donepezil hydrochloride and/or its metabolites can be

eliminated by dialysis (hemodialysis, peritoneal dialysis or hemofiltration).

Memantine hydrochloride

Experience with overdose obtained in clinical studies or post-marketing is limited.

Symptoms: Relatively large overdoses (200 mg and 105 mg per day for 3 days, respectively) have been associated with either only symptoms of fatigue, weakness and/or diarrhea or no symptoms. Patients taking the drug below 140 mg or in unknown doses have shown symptoms originating from the central nervous system (confusion, drowsiness, somnolence, vertigo, agitation, aggression, hallucinations and gait disturbances) and/or gastrointestinal (vomiting and diarrhea).

In the most extreme case of overdose, the patient survived with effects on the central nervous system (coma for 10 days, followed by diplopia and agitation) after oral ingestion of a total of 2000 mg of memantine. The patient received symptomatic treatment and plasmapheresis. The patient recovered without permanent sequelae.

In another case of major overdose, the patient survived and recovered. The patient took 400 mg memantine orally. The patient experienced central nervous system symptoms such as restlessness, psychosis, visual hallucinations, proconvulsivity, somnolence, stupor, and loss of consciousness.

Treatment: In case of overdose, treatment should be symptomatic. There is no specific antidote for poisoning or overdose. Standard clinical procedures to remove drug substance, e.g. gastric lavage, activated charcoal (inhibition of potential entero-hepatic reflux), acidification of urine, forced diuresis should be used as appropriate.

If signs or symptoms of general central nervous system hyperstimulation are present, careful symptomatic clinical treatment should be considered.

PHARMACOLOGICAL FEATURES

5.1. Pharmacodynamic features:

Pharmacotherapeutic Group

Anti-dementia drugs, Anticholinesterases ATC code: N06DA52

Donepezil hydrochloride

Mechanism of action

Donepezil hydrochloride is a selective and reversible inhibitor of acetylcholinesterase, which is the predominant cholinesterase in the brain. Donepezil hydrochloride is a 1000-fold more potent inhibitor of this enzyme in vitro than butyrylcholinesterase, an enzyme found primarily outside the central nervous system.

Clinical Studies

Mild and Moderate Alzheimer's Disease

In clinical studies involving patients with Alzheimer's type dementia, daily use of 5 mg and 10 mg donepezil hydrochloride caused a steady-state inhibition of acetylcholine activity (measured in erythrocyte membranes) of 63.6% and 77.3%, respectively. Inhibition of red blood cell acetylcholinesterase (AChE) by donepezil hydrochloride has been shown to be consistent with changes in ADAS-Cog, a sensitive scale examining selected aspects of cognitive function. No studies have been conducted on the potential of donepezil hydrochloride to alter the course of underlying neuropathology. For this reason, donepezil is not thought to have an effect on the progression of the disease.

The effectiveness of donepezil in the treatment of Alzheimer's type dementia was investigated in four placebo-controlled studies (2 studies of 6 months duration and 2 studies of 1 year duration). In clinical studies, an analysis was performed as a result of 6 months of donepezil treatment. Three effectiveness criteria were used together in this analysis. ADAS-cog, clinician's interview-based impression of change based on information from the patient's relative (CIBIC+ - measures global functions), Activities of Daily Living Subscale of the Clinical Dementia Measurement Scale (CDR - measures skills in social environments, at home, hobbies and personal care).

Patients who met the characteristics listed below were considered to have responded to treatment.

Answer = Improvement of at least 4 points in ADAS-Cog

No worsening in CIBIC+

No worsening in the Activities of Daily Living Subscale of the Clinical Dementia Measurement Scale

	% Answer	
	Population intended to be treated N=365	Evaluation Population N=352
Plasebo group	% 10	% 10
Group using 5 mg donepezil hydrochloride	% 18 *	% 18 *
Group using 10 mg donepezil hydrochloride	% 21 *	% 22 **

* p < 0.05

** p < 0.01

Donepezil produced a statistically significant dose-dependent increase in the percentage of patients judged to respond to treatment.

Memantin hidroklorür

Mechanism of Action

There is increasing evidence that glutamatergic neurotransmission dysfunction, especially in N-methyl-D-aspartate (NMDA) receptors, contributes to the manifestation of symptoms and disease progression in neurodegenerative dementias.

Memantine hydrochloride is an antidementia drug. It is a voltage-dependent, medium-affinity and non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist. Memantine hydrochloride modulates the effects of pathologically elevated tonic glutamate levels leading to neuronal dysfunction.

Clinical Studies

A pivotal monotherapy study in moderate to severe Alzheimer's patients (MMSE-Mini mental state examination initial total scores of 3-14) included 252 outpatients. The study showed beneficial effects of memantine treatment compared to placebo at 6 months (CIBIC-plus (Clinician's impression of change based on interview): $p=0.025$; ADCS-ADLsev (Alzheimer's Disease Collaborative Study-Activities of daily living): $p=0.003$; SIB - Analysis of observed cases for severe destruction scale $p=0.002$).

403 patients were included in the pivotal monotherapy study of memantine for the treatment of mild to moderate Alzheimer's disease (MMSE baseline total scores of 10 – 22). Memantine-treated patients showed statistically significantly better efficacy than placebo-treated patients for the following primary endpoints: ADAS-cog (Alzheimer's disease assessment scale) at week 24 (LOCF-Last observation carried forward) ($p=0.003$) and CIBIC-plus ($p=0.004$). A total of 470 patients (MMSE baseline total scores 11 – 23) were randomized to another monotherapy study of mild to moderate Alzheimer's Disease. In the prospectively defined primary analysis, no statistically significant value was reached at the primary efficacy endpoint at week 24. A meta-analysis of patients in 6 different phase III, placebo-controlled, 6-month studies (including monotherapy studies and studies in patients receiving a stable dose of acetylcholinesterase inhibitors) in patients with moderate to severe Alzheimer's disease (MMSE total scores <20) found that memantine treatment improved cognitive impairment. showed a statistically significant better effect in global and functional areas. When patients were identified with concurrent worsening in these three domains, the results showed that the anti-worsening effect of memantine was statistically significant, with many patients given placebo experiencing twice as much worsening as memantine-treated patients (21% vs 11%, $p<0.0001$).

5.2 Pharmacokinetic properties

General features

Donepezil hydrochloride

Absorption:

Maximum plasma levels are reached approximately 3 to 4 hours after oral ingestion. Plasma concentrations and area under the curve increase in proportion to the dose. Since its half-life is approximately 70 hours, it gradually reaches steady state by taking a single daily dose regularly. Approximate steady state is reached within 3 weeks after starting treatment. Once steady state is

reached, plasma concentrations of donepezil hydrochloride and its associated pharmacodynamic activity vary little during the day. Donepezil hydrochloride absorption is not affected by food.

Distribution:

Donepezil hydrochloride is approximately 95% bound to plasma proteins. Plasma protein binding of the active metabolite, 6-O-desmethyldonepezil, is unknown. The distribution of donepezil hydrochloride in various body tissues has not been precisely studied. However, in a mass balance study in healthy male volunteers, approximately 28% of the drug was not released 240 hours after ingestion of a single 5 mg dose of ¹⁴C-labeled donepezil hydrochloride. This indicates that donepezil hydrochloride and/or its metabolites may persist in the body for more than 10 days.

Biotransformation:

Donepezil hydrochloride is converted by the cytochrome P450 system (especially CYP3A4 and, to a lesser extent, CYP2D6 isoenzymes) into a large number of metabolites, not all of which are yet complete. Following a single 5 mg dose of ¹⁴C-labelled donepezil hydrochloride, plasma radioactivity expressed as a percentage of the dose taken was essentially intact donepezil hydrochloride (30%), activity similar to that of 6-O-desmethyl donepezil (11%-donepezil hydrochloride). (the only metabolite showing this), donepezil-cis-N-oxide (9%), 5-O-desmethyl donepezil (7%), 5-O-desmethyl donepezil glucuronide conjugate (3%) were determined.

Elimination:

Approximately 57% of the ingested dose of donepezil hydrochloride was excreted in the urine (17% was unchanged donepezil), while 14.5% was excreted in the feces, indicating that biotransformation and urinary excretion are the main routes of excretion. There is no evidence to suggest that donepezil hydrochloride and/or any of its metabolites enter the enterohepatic circulation. Plasma half-life is approximately 70 hours.

Memantine hydrochloride Absorption:

Memantine has an absolute bioavailability of approximately 100%, with a t_{max} of 3-8 hours. No effects of food on the absorption of memantine hydrochloride have been reported.

Distribution:

With daily doses of 20 mg, steady-state plasma concentrations of 70-150 ng/ml (0.5-1 µmol) have been achieved, varying widely from person to person. When daily doses of 5-30 mg were taken, the mean cerebrospinal fluid (CSF)/serum ratio was calculated to be 0.52. The volume of distribution is approximately 10 L/kg. 45% of memantine hydrochloride is bound to plasma proteins.

Biotransformation:

After oral administration of memantine hydrochloride, 80% is found unchanged in the blood. The major major metabolites of memantine hydrochloride in humans are N-3,5-dimethyl-gludantan, the isomeric mixture of 4- and 6-hydroxy-memantine, and 1-nitroso-3,5-dimethyl-adamantane. None of these metabolites have NMDA-antagonist activity. In in vitro studies, no reaction catalyzed by the cytochrome P450 enzyme system was detected. In a study with ¹⁴C-memantine hydrochloride, approximately 84% of an orally administered dose of memantine hydrochloride was detected in the urine within 20 days, with more than 99% occurring renally.

Elimination:

Memantine hydrochloride terminal half-life ($t_{1/2}$) is 60-100 hours. It is eliminated monoexponentially. In studies in volunteers with normal renal function, total clearance increased up to 170 ml/min/1.73 m². A portion of total renal clearance is achieved by tubular secretion. Renal clearance also involves tubular reabsorption, possibly via cationic carrier proteins. In the case of alkaline urine, the renal elimination rate of memantine hydrochloride may be reduced by a factor of 7-9. (see Section 4.4). Alkalinization of the urine may occur as a result of a radical change in diet (such as a switch from a carnivorous to a vegetarian diet) or the ingestion of large amounts of alkalising gastric buffers.

Linearity/non-linearity:

In studies conducted on volunteers, it was found to show linear pharmacokinetics at doses of 10-40 mg.

Pharmacokinetic/pharmacodynamic relationship:

At a dose of 20 mg memantine per day, cerebrospinal fluid (CSF) levels meet the K_i value (K_i = inhibition constant) of memantine in the frontal cortex of 0.5 μ mol.

Characteristic features of patients

Gender, race, and smoking habit have no significant clinical effect on donepezil hydrochloride plasma concentrations. The pharmacokinetics of donepezil have not been fully studied in healthy elderly patients, patients with Alzheimer's disease, or patients with vascular dementia. However, mean plasma levels in patients are close to those in healthy young volunteers.

In patients with mild or moderate hepatic impairment, increased steady-state concentrations of donepezil have been observed; 48% on average AUC, 39% on average C_{max} (See Section 4.2).

5.2 Preclinical safety data**Donepezil hydrochloride**

Extensive experiments in experimental animals have shown that this compound has little effect other than its intended cholinergic stimulating effect (see section 4.9).

Donepezil was not found to be mutagenic in bacterial and mammalian cell mutation analyses. In vitro, some clastogenic effects were observed at concentrations extremely toxic to cells and up to 3000 times higher than steady-state plasma concentrations, but no clastogenic or other genotoxic effects were observed in the in vivo mouse micronucleus model.

No evidence of the oncogenic potential of donepezil was obtained in long-term carcinogenicity studies conducted in rats and mice.

Donepezil hydrochloride had no effect on fertility in rats and was not found to be teratogenic in rats/mice; However, in pregnant rats administered drug at approximately 50 times the human dose, there was an increase in stillbirths and a slight effect on the number of surviving offspring after

birth.

Memantine hydrochloride

In short-term studies in rats, other NMDA-antagonists such as memantine produced neuronal vacuolization and necrosis (Olney lesions) only after doses that resulted in very high serum concentrations. Ataxia and other preclinical signs appear before vacuolization and necrosis. Since these effects were not observed in long-term studies in rodent and non-rodent experimental animals, the clinical relevance of these findings is unknown.

In repeated dose toxicity studies, ocular changes were observed in rodents and dogs, but not in monkeys. Clinical with memantine

In the studies, specific ophthalmoscopic examinations did not reveal any ocular changes.

Phospholipidosis in pulmonary macrophages due to memantine accumulation in lysosomes has been observed in rodents. This effect is also seen with other drugs with cationic amphiphilic properties. It is possible that there is a relationship between this accumulation and the vacuolization seen in the lungs. The effect is seen in rodents only at high doses. The clinical relevance of these findings is unknown.

As a result of standard experiments with memantine, no genotoxicity was observed. There was no evidence of carcinogenicity in lifetime studies in mice and rats.

Memantine was not teratogenic in rats and rabbits, even at maternally toxic doses, and no adverse effects on productivity were detected.

Fetal growth was observed to be reduced in rats at doses equivalent to or slightly higher than those administered to humans.

5 PHARMACEUTICAL PROPERTIES

6.1 List of excipients

Laktoz monohidrat (sıgır kaynaklı)

Mikrokristalin selüloz

Colloidal silicon dioxide

crospovidone

Talc

sodium stearyl fumarate

polyvinyl alcohol

titanium dioxide

polyethylene glycol

Red iron oxide

Black iron oxide

6.1 Incompatibilities

Not valid.

6.2 Shelf life

24 months

6.3 Special precautions for storage

Store in its packaging at room temperature below 25°C.

6.4 Nature and content of packaging

28 and 84 film-coated tablets are packaged in transparent PVC/PE/PVDC/Al foil blister packaging in a cardboard box with instructions for use.

6.5 Disposal of residues of the medicinal product for human use and other special measures

Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulations".

MARKETING AUTHORISATION HOLDER

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