SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

REMEMBA 10 mg/10 mg dispersible tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Donepezil hydrochloride 10 mg

Memantine hydrochloride 10 mg

Excipients:

Sucralose 12,5 mg

Sorbitol 17,5 mg

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablet

White, round, biconvex dispersible tablets with “1010” printed on one side

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

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

4.2. Posology and method of administration

Posology/administration frequency and duration:

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

Adults/Elderly: Treatment is started with 5/5 mg/day (single dose daily). REMEMBA should be taken orally in the evening just before going to bed. The 5/5 mg/day dose should be continued for at least 4–6 weeks to obtain the earliest clinical response to treatment and to reach steady-state concentrations of REMEMBA. After 4–6 weeks of treatment with 5/5 mg/day, the

REMEMBA dose can be increased to 5/10 mg/day or 5/20 mg/day or 10/10 mg/day or 10/20 mg/day (single dose daily), depending on the patient's donepezil hydrochloride and memantine hydrochloride needs. The highest recommended daily dose of donepezil hydrochloride is 10 mg. The highest recommended daily dose of memantine hydrochloride is 20 mg.

Method of Application:

REMEMBA is for oral use. REMEMBA is taken every night before going to bed. The tablets can be swallowed with a glass of water.

In patients who have difficulty swallowing, the tablets can be administered by dispersing them in 1 glass of water (100-200ml). The tablet disperses rapidly in the water and is mixed to form a thin suspension in the water. After the suspension is drunk, any residue that may remain in the glass should be resuspended with a small amount of water and drunk. The tablets can also be dispersed in a tablespoon of water and administered directly.

Dispersible tablets should be taken only with water and should not be mixed with milk or fruit juice.

Additional information on special populations:

Kidney failure:

No dosage adjustment of donepezil is required in patients with renal insufficiency. No dosage adjustment of memantine hydrochloride is required in patients with mild renal insufficiency (creatinine clearance 50-80 ml/min). In patients with moderate renal insufficiency (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 may be increased to 20 mg according to the standard titration scheme. For patients with severe renal insufficiency (creatinine clearance 5-29 ml/min), the daily dose of memantine hydrochloride should be 10 mg.

Liver failure:

In mild and moderate hepatic impairment, the dose of donepezil should be gradually increased according to the patient's tolerance due to the possibility of longer exposure to the drug. Studies with 10 patients with stable alcoholic cirrhosis showed that the clearance of donepezil hydrochloride was reduced by 20%. There is no data on the use of donepezil hydrochloride in patients with severe hepatic impairment.

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

Pediatric Population:

The safety and effectiveness of REMEMBA in children and adolescents have not been established. Therefore, its use in children under 18 years of age is not recommended.

Geriatric Population:

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

4.3. Contraindications

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

4.4. Special warnings and precautions for use

Donepezil hydrochloride

Treatment should be initiated and directed by a physician experienced in diagnosing and treating Alzheimer's dementia. The diagnosis should be made according to accepted guidelines (e.g. DSM IV, ICD 10). Donepezil treatment should only be initiated when there is a responsible person who can regularly monitor the patient's medication intake. Treatment should continue as long as the patient is receiving therapeutic benefit from the drug. Therefore, the clinical advantages of donepezil should be re-evaluated at regular intervals. A decision should be made to discontinue the drug when there is no longer any evidence of a therapeutic effect. Individual responses to donepezil cannot be predicted.

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

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

Cardiovascular Conditions: Because of their pharmacologic effects, cholinesterase inhibitors may have a vagotonic effect on heart rate (such as bradycardia). The potential for this effect may be particularly important in patients with “sick sinus syndrome” or other supraventricular

cardiac conduction conditions such as sinoatrial or atrioventricular block. There have been reports of syncope and convulsions. Heart block or prolonged sinus pause should be considered when evaluating these patients.

Gastrointestinal Conditions: Cholinomimetics may increase gastric acid production. 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, no increased incidence of peptic ulcers or gastrointestinal bleeding was demonstrated in clinical studies comparing donepezil to placebo.

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

Central Nervous System: Convulsions: Cholinomimetics are believed to have the potential to cause generalized convulsions. However, convulsions may also be indicative of Alzheimer's disease. Cholinomimetics have the potential to induce or potentiate extrapyramidal symptoms.

Pulmonary System: Because of cholinomimetic effects, cholinesterase inhibitors should be used with caution in patients with a history of asthma or obstructive pulmonary disease. Donepezil should not be used concomitantly with other acetylcholinesterase inhibitors, cholinergic agonists or antagonists.

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

Mortality in vascular dementia clinical trials: Three 6-month clinical trials were conducted that included individuals who met NINDS-AIREN criteria for probable or possible vascular dementia (VaD). The NINDS-AIREN criteria were designed to identify patients whose dementia was due solely to vascular causes and to exclude patients with Alzheimer's disease.

The 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. The 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. The mortality rates in the third study were 11/648 (1.7%) for 5 mg donepezil hydrochloride and 0/326 (0%) for placebo.

When mortality data from these three VaD studies were combined, the mortality rate in the donepezil hydrochloride group (1.7%) was 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 receiving donepezil hydrochloride or placebo was determined to have various vascular causes, an expected result in an elderly population with underlying vascular disease.

Analysis of fatal and nonfatal 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 when 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.

Neuroleptic Malignant Syndrome (NMS) is a life-threatening disease and is characterized by hyperthermia, muscle rigidity, autonomic instability, altered state of consciousness, and elevated serum creatine phosphokinase levels; in addition, myoglobinuria (rhabdomyolysis) and acute renal failure may also occur.

NMS associated with donepezil use has been reported rarely, especially in patients receiving concomitant antipsychotics.

If a patient presents with symptoms suggestive of NMS or develops unexplained high fever in the absence of other clinical manifestations of NMS, donepezil treatment should be discontinued.

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-antagonists such as dextromethorphan and ketamine. Since these compounds act on the same receptor as memantine hydrochloride, possible side effects (especially those related to the central nervous system) may be more frequent or stronger (see 4.5 Interactions with other medicinal products and other forms of interaction).

The patient may need to be carefully monitored if there are factors that increase urine pH (see 5.2 Pharmacokinetic properties). These factors include a radical change in diet (e.g. from a carnivore to a vegetarian diet) or a large intake of alkalizing gastric buffers. Urine pH may

also increase with renal tubular acidosis (RTA) or serious urinary tract infections caused by Proteus bacteria.

In many clinical studies, patients with recent myocardial infarction, uncompensated congestive heart failure (New York Heart Association (NYHA) index III-IV), or uncontrolled hypertension were excluded. Since insufficient data are available, patients with these conditions should be kept under close observation.

Warning for Sucralose
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not use this medication.
Warning for Sorbitol
Patients with rare hereditary problems of fructose intolerance should not use this medication.

4.5. Interactions with other medicinal products and other forms of interaction

Donepezil hydrochloride

Clinical experience with donepezil is limited, therefore, not all possible interactions may have been recorded. The prescribing physician should be aware of the possibility of new interactions with donepezil that are currently unknown.

Donepezil hydrochloride and/or any of its metabolites do not inhibit the metabolism of theophylline, warfarin, cimetidine, digoxin, thioridazine, risperidone and sertraline in humans. The metabolism of donepezil hydrochloride is not affected by concomitant administration of digoxin, cimetidine, thioridazine, risperidone and sertraline.

In a study of Parkinson's disease patients receiving optimal treatment with L-Dopa/carbidopa, 21 days of donepezil hydrochloride administration had no effect on blood levels of L-Dopa or carbidopa. No effect on motor activity was seen in this study.

In vitro studies have shown that cytochrome P450 isoenzyme 3A4 and to a lesser extent isoenzyme 2D6 are involved in the metabolism of donepezil. In vitro drug interaction studies show that ketoconazole, a CYP3A4 inhibitor, and quinidine, a CYP2D6 inhibitor, inhibit donepezil metabolism. Therefore, these and other CYP3A4 inhibitors (such as itraconazole and erythromycin) and CYP2D6 inhibitors (such as fluoxetine) may inhibit donepezil metabolism. Ketoconazole increases mean donepezil concentrations by 30%. Enzyme inducers such as rifampicin, phenytoin, carbamazepine and alcohol may decrease donepezil levels. Such drug combinations should be used with caution, as the significance of the inhibitory or inducing effect is unknown. Donepezil has the potential to interact with drugs having anticholinergic

activity. There is also the potential for synergistic activity with concomitant therapy with drugs such as succinicoline, other nerve and muscle blocking agents or cholinergic agonists, or beta-blocking agents that have effects on cardiac conduction.

St. Johns Wort may have a decreasing effect on REMEMBA levels.

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 increased when used with NMDA antagonists such as memantine. It may reduce the effects of barbiturates and neuroleptics. The use of memantine with antispasmodic agents, dantrolene or baclofen may modify their effects and require dosage adjustment.
- The use of memantine with amantadine should be avoided because of the risk of pharmacotoxic psychosis. Both substances are NMDA-antagonists. The same approach may be valid for ketamine and dextromethorphan. There is one published case report of 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, causing a risk of increased plasma levels.
- If memantine is used concomitantly with hydrochlorothiazide (HCT) or any combination with HCT, a decrease in HCT serum level is likely.
- In post-marketing experience, isolated cases of increased INR (International Normalized Ratio) have been reported in patients receiving memantine concomitantly with warfarin. Although a causal relationship has not been established, close monitoring of prothrombin time or INR is recommended for patients receiving concomitant oral anticoagulants.
- Clearance may be decreased when used with carbonic anhydrase inhibitors and sodium bicarbonate.

No significant drug interaction was observed between memantine and glyburide/metformin combination or donezepil in single-dose pharmacokinetic studies in healthy young volunteers.

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

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

Additional information on special population:

No interaction studies regarding special populations were identified.

Pediatric population:

No interaction studies in the pediatric population have been identified.

4.6. Pregnancy and lactation

General advice

Pregnancy category: C

Women of childbearing potential / Contraception

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

Pregnancy period

There are insufficient data on the use of donepezil in pregnancy. Animal studies have not shown teratogenic effects, but perinatal and postnatal toxicity has been observed. The potential risk for humans is unknown.

There are no or limited data on the use of memantine in pregnancy.

Animal studies indicate that memantine causes a reduction in intrauterine growth at exposure levels equal to or slightly higher than those in humans. The potential risk for humans is unknown.

There are no sufficient data on the use of donepezil hydrochloride + memantine hydrochloride combination in pregnant women.

Animal studies are insufficient regarding effects on pregnancy/embryonal/fetal development/birth or postnatal development.

The potential risk to humans is unknown. REMEMBA should not be used during pregnancy unless absolutely necessary.

Lactation period

Although donepezil contained in REMEMBA is excreted in breast milk in rats, there is no information on whether the drug is excreted in human breast milk. There is no information on the passage of memantine into human milk. However, due to the lipophilicity of memantine, this is likely to occur. REMEMBA should not be used in nursing mothers.

Reproductive ability/ Fertility

Animal studies of donepezil hydrochloride have shown no reproductive toxicity (see also section 5.3).

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

4.7. Effects on the ability to drive and use machines

Alzheimer's dementia may cause deterioration in driving performance or may reduce the ability to use machines. In addition, REMEMBA may cause weakness, dizziness and muscle cramps, especially at the beginning or during dose increases. The ability of Alzheimer's patients treated with REMEMBA who continue to drive or use machines should be regularly evaluated by the treating physician. REMEMBA may slightly or moderately impair the ability to drive or use machines.

4.8. Undesirable effects

Adverse drug reactions are listed by frequency as defined below:

Very common (≥1/10); common (≥1/100 ila <1/10); uncommon (≥1/1.000, ila <1/100); rare (≥1/10.000, <1/1.000); very rare (<1/10.000), unknown (cannot be estimated from the available data.)

Donepezil hydrochloride

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

Infections and infestations

Common: Common cold

Metabolism and nutritional disorders

Common: Anorexia

Psychiatric disorders

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

Nervous system disorders

Common: Syncope*, dizziness, insomnia

Uncommon: Seizures*

Rare: Extrapyramidal symptoms

Very rare: Neuroleptic malignant syndrome

Cardiac disorders

Uncommon: Bradycardia

Rare: Sinoatrial block, atrioventricular block

Gastrointestinal disorders

Very common: Diarrhea, nausea

Common: Vomiting, abdominal discomfort

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

Hepatobiliary disorders

Rare: Liver dysfunction including hepatitis**

Skin and subcutaneous tissue disorders

Common: Rash, pruritus

Musculoskeletal, connective tissue and bone disorders

Common: Muscle cramps

Very rare: Rhabdomyolysis****

Kidney and urinary disorders

Common: Urinary incontinence

General disorders and conditions related to the application area

Very common: Headache

Common: Fatigue, pain

Investigations

Uncommon: Minor increases in serum muscle creatine kinase concentrations

Injury and poisoning

Common: Accident

* The possibility of heart block or prolonged pauses in sinus rhythm should be considered in the evaluation of patients for syncope or seizures (see section 4.4).

** Reports of hallucinations, abnormal dreams, nightmares, agitation and aggressive behaviour have resolved with dose reduction or discontinuation of therapy.

*** In the event of unexplained liver dysfunction, discontinuation of Remembá should be considered.

**** The possibility of a close temporal relationship to the initiation of donepezil therapy or dose increase independent of rhabdomyalysis, Neuroleptic Malignant Syndrome should be considered.

Memantine

In clinical trials of mild, moderate, and severe dementia in 1,784 patients treated with memantine and 1,595 patients treated with placebo, the overall incidence of adverse events with memantine did not differ from those with placebo; adverse events were generally mild to moderate in severity. The most common adverse events with a higher incidence in the memantine group than in the placebo group were dizziness (6.3% vs. 5.6%), headache (5.2% vs. 3.9%), constipation (4.6% vs. 2.6%), somnolence (3.4% vs. 2.2%), and hypertension (4.1% vs. 2.8%).

Infections and infestations

Uncommon: Fungal infections

Immune system disorders

Common: Hypersensitivity

Psychiatric disorders

Common: Somnolence

Uncommon: Confusion, hallucination[1]

Unknown: Psychotic reactions[2]

Nervous system disorders

Common: Dizziness, balance disorder

Uncommon: Gait abnormality

Very rare: Seizures

Cardiac diseases

Uncommon: Heart failure

Vascular diseases

Common: Hypertension

Uncommon: Venous thrombosis/thromboembolism

Respiratory, thoracic and mediastinal disorders

Common: Dyspnea

Gastrointestinal disorders

Common: Constipation

Uncommon: Vomiting

Unknown: Pancreatitis[2]

Hepatobiliary disorders

Common: Increased liver function test

Unknown: Hepatitis

General disorders and administration site conditions

Common: Headache

Uncommon: Fatigue

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

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

[2] Isolated case reports post-marketing.

4.9. Overdose and its treatment

Donepezil hydrochloride

The expected median lethal doses of a single oral dose of donepezil hydrochloride in mice and rats are 45, 32, and 15 mg/kg, respectively, which are approximately 225, 160, and 75 times the maximum recommended human dose of 10 mg. Dose-related signs of cholinergic stimulation have been observed in animals and include decreased spontaneous movement, prone position, staggering gait, 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 possible, and if the respiratory muscles are involved, death may result.

As in all cases of overdose, general supportive measures should be used. In case of overdose of donepezil hydrochloride, tertiary anticholinergics such as atropine may be used as antidotes. Intravenous administration of atropine sulphate 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 are removed by dialysis (haemodialysis, peritoneal dialysis or haemofiltration).

Memantine hydrochloride

Overdose experience from clinical trials or post-marketing is limited.

Symptoms: Relatively large overdoses (200 mg and 105 mg daily for 3 days, respectively) have been associated with either only symptoms of fatigue, weakness, and/or diarrhea, or no symptoms at all. Patients who received less than 140 mg or unknown doses have experienced symptoms of central nervous system (confusion, somnolence, drowsiness, vertigo, agitation, aggression, hallucinations, and gait disturbances) and/or gastrointestinal (vomiting and diarrhea) origin.

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

permanent sequelae. In another major overdose case, the patient survived and recovered. The patient ingested 400 mg of memantine orally. The patient experienced CNS symptoms of restlessness, psychosis, visual hallucinations, proconvulsiveness, 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 (interruption of potential entero-hepatic recirculation), acidification of urine, forced diuresis should be used as appropriate. If signs or symptoms of general central nervous system overstimulation are present, careful symptomatic clinical treatment should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Anti-dementia Drugs, Anticholinesterases

ATC code: N06DA52

Donepezil hydrochloride

Mechanism of action

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

Clinical studies

Mild to moderate Alzheimer's disease

In clinical studies in patients with Alzheimer's type dementia, single daily doses of 5 mg and 10 mg of donepezil hydrochloride produced steady-state inhibition of acetylcholinesterase activity (measured in erythrocyte membranes) of 63.6% and 77.3%, respectively, following dosing. Inhibition of acetylcholinesterase (AChE) in red blood cells by donepezil hydrochloride was shown to correlate with changes in ADAS-Cog, a sensitive measure of selected aspects of cognitive function. The potential for donepezil hydrochloride to alter the course of the underlying neuropathology has not been studied. Therefore, donepezil is not thought to have an effect on disease progression.

The efficacy of donepezil in the treatment of Alzheimer's dementia was investigated in four placebo-controlled studies (2 studies of 6 months duration and 2 studies of 1 year duration).
In the clinical studies, an analysis was performed on the results of 6 months of donepezil treatment. In this analysis, 3 efficacy criteria were used together. ADAS-cog, clinician's impression of change based on interview information from the patient's relative (CIBIC+ - measures global functions), Clinical Dementia Rating Scale Activities of Daily Living Subscale (CDR - measures skills in social environments, 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 on ADAS-Cog
No deterioration on CIBIC+
No deterioration on Activities of Daily Living
Subscale of Clinical Dementia Rating Scale

	Answer %	
	Population intended to be treated N= 365	Population evaluated N= 352
Placebo group	10 %	10 %
Donepezil 5 mg group	18 %*	18 %*
Donepezil 10 mg group	21 %*	22 %**

*p < 0,05
** p < 0,01

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

Memantine hydrochloride
Mechanism of action
There is increasing evidence that dysfunction of glutamatergic neurotransmission at 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, non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist. Memantine hydrochloride blocks the effects of pathologically elevated tonic glutamate levels that lead to neuronal dysfunction.

Long-term elevated glutamate levels in the brains of dementia patients prevent Mg+2 ions from blocking voltage-dependent NMDA receptors, causing a continuous influx of Ca+2 ions into the cell, thus leading to neuronal degeneration. Studies have shown that memantine hydrochloride binds to NMDA receptors more effectively than Mg+2 ions, thus effectively blocking the influx of Ca+2 ions through the NMDA channel while preserving the transient physiological activation of the channels by high concentrations of synaptically released glutamate.

Clinical Studies

A pivotal monotherapy study in patients with moderate to severe Alzheimer's disease (initial total scores of the Mini Mental State Examination-MMSE 3-14) enrolled 252 outpatients. The study demonstrated beneficial effects of memantine treatment over placebo at 6 months (Clinician's Impression of Change Based on Interview (CIBIC-plus): p=0.025; Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADLsev): p=0.003; Analysis of observed cases for Severe Impairment Scale-SIB p=0.002).

A pivotal monotherapy study of memantine for the treatment of mild to moderate Alzheimer's disease (MMSE baseline total scores of 10 to 22) enrolled 403 patients. Memantine-treated patients showed statistically significantly better efficacy than placebo-treated patients for the following primary endpoints at week 24 (Last Observation Carried Forward - LOCF), ADAS-cog (p=0.003) and CIBIC-plus (p=0.004). A total of 470 patients (MMSE baseline total scores of 11 to 23) were randomized to another monotherapy study in mild to moderate Alzheimer's disease. In the prospectively defined primary analysis, statistical significance was not reached for the primary efficacy endpoint at week 24.

A meta-analysis of 6 phase III, placebo-controlled, 6-month studies (including monotherapy studies and studies of patients on a stable dose of acetylcholinesterase inhibitors) in patients with moderate to severe Alzheimer's disease (MMSE total scores <20) showed that memantine treatment resulted in statistically significant superior effects in cognitive, global, and functional domains. When patients were identified with concurrent deterioration in these three domains, the results showed that memantine had a statistically significant effect on preventing

deterioration, with twice as many placebo-treated patients experiencing deterioration 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 administration. Plasma concentrations and area under the curve increase in proportion to the dose. Since the half-life is approximately 70 hours, steady state is gradually reached with regular single daily dosing. Approximate steady state is reached within 3 weeks of initiating therapy. Once steady state is reached, plasma concentrations of Donepezil hydrochloride and its associated pharmacodynamic activity show little change over the course of days. Absorption of Donepezil Hydrochloride is not affected by food.

Distribution:

Donepezil hydrochloride is approximately 95% bound to plasma proteins. The plasma protein binding of the active metabolite, 6-O-desmethyldonepezil, is unknown. The distribution of donepezil hydrochloride in various body tissues has not been studied conclusively. However, in a mass balance study in healthy male volunteers, approximately 28% of the drug remained unrecovered 240 hours after ingestion of a single 5 mg dose of 14C-labeled donepezil hydrochloride. This suggests 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 numerous metabolites, not all of which are yet complete. After ingestion of a single 5 mg dose of 14C-labeled donepezil hydrochloride, plasma radioactivity expressed as a percentage of the ingested dose was determined as mainly intact donepezil hydrochloride (30%), 6-O-desmethyl donepezil (11% - the only metabolite with activity similar to donepezil hydrochloride), donepezil-cis-N-oxide (9%), 5-O-desmethyl donepezil (7%), 5-O-desmethyl donepezil glucuronide conjugate (3%).

Elimination:

Approximately 57% of the administered dose was excreted in the urine (17% unchanged donepezil) and 14.5% in the feces, indicating that biotransformation and urinary excretion are

the main routes of elimination. There is no evidence to suggest that donepezil hydrochloride and/or any of its metabolites undergo enterohepatic circulation. The plasma half-life is approximately 70 hours.

Linearity/Nonlinearity:

Plasma concentrations and area under the curve increase in proportion to dose. Steady-state concentrations were increased in patients with mild to moderate hepatic impairment, with a 48% increase in mean AUC and a 39% increase in mean Cmax.

Characteristics in patients

Gender, race and smoking habits have no clinically significant effect on plasma concentrations of donepezil hydrochloride. 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 similar to those in healthy young volunteers.

In patients with mild or moderate hepatic impairment, steady-state concentrations of donepezil were increased, with an average of 48% in AUC and a mean of 39% in Cmax (see section 4.2 Dosage and administration).

Memantine hydrochloride

Absorption:

The absolute bioavailability of oral memantine hydrochloride is approximately 100% with a Tmax of 3-8 hours. No effect of food on the absorption of memantine hydrochloride has 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, with considerable variation from person to person. With daily doses of 5-30 mg, the mean cerebrospinal fluid (CSF)/serum ratio has been calculated as 0.52. The volume of distribution is approximately 10 L/kg. Memantine hydrochloride is 45% bound to plasma proteins.

Biotransformation:

After oral administration of memantine hydrochloride, 80% of it is found in the blood unchanged. The main metabolites of memantine hydrochloride are N-3.5-dimethyl-gludantane,

4- and 6-hydroxy-memantine isomeric mixture and 1-nitroso-3.5-dimethyl-adamantane. None of these metabolites have NMDA-antagonist activity. In vitro studies have not detected any reactions catalyzed by the cytochrome P450 enzyme system. In a study conducted with oral 14C-memantine hydrochloride, it was determined that approximately 84% of the dose was recovered within 20 days and more than 99% was renally excreted.

Elimination:

Memantine hydrochloride terminal half-life (t1/2) is 60-100 hours. It is eliminated monoexponentially. In studies performed on volunteers with normal renal function, total clearance was increased up to 170 ml/min/1.73 m2. Part of the total clearance is provided by tubular secretion. Renal clearance is probably by tubular reabsorption via cationic carrier proteins. Renal elimination of memantine hydrochloride may be reduced 7-9 fold in alkaline urine. Alkalinization of urine may occur as a result of radical change in diet (e.g. from carnivore to vegetarian diet) or by the ingestion of large amounts of alkalizing gastric buffers.

Linearity/non-linearity:

Studies in volunteers have shown linear pharmacokinetics at doses of 10-40 mg.

Pharmacokinetic/pharmacodynamic relationship:

At a dose of 20 mg memantine per day, cerebrospinal fluid (CSF) levels match the ki value (ki = inhibition constant) of memantine, which is 0.5 μmol in the frontal cortex.

5.3. Preclinical safety data

Donepezil hydrochloride

General

Extensive animal testing has shown that this compound has little effect other than its intended cholinergic stimulatory effect (see section 4.9).

Mutagenicity

Donepezil was not mutagenic in bacterial and mammalian cell mutation assays.

Some clastogenic effects were observed in vitro at concentrations extremely toxic to cells and 3000-fold greater than steady-state plasma concentrations, but no clastogenic or other genotoxic effects were observed *in the in vivo* maouse micronucleus model.

Long-term carcinogenicity studies in rats and mice provided no evidence of oncogenic potential of donepezil.
Donepezil hydrochloride had no effects on fertility in rats and was not teratogenic in rats or rabbits; however, in pregnant rats administered approximately 50 times the human dose, there was an increase in stillbirths and a slight effect on the number of surviving pups.

Memantine hydrochloride
In short-term studies in rats, other NMDA-antagonists, such as memantine, have produced neuronal vacuolization and necrosis (Olney lesions) only after doses that produced very high serum concentrations. Ataxia and other preclinical signs appear before vacuolization and necrosis. The clinical relevance of these findings is unknown, as these effects have not been seen in long-term studies in rodent or nonrodent animals.
Ocular changes were observed in rodents and dogs in repeat-dose toxicity studies, but not in monkeys. Specific ophthalmoscopic examinations in clinical studies with memantine did not reveal any ocular changes.
Phospholipidosis in pulmonary macrophages related to accumulation of memantine in lysosomes has been observed in rodents. This effect is also seen with other cationic amphiphilic drugs. A relationship between this accumulation and vacuolization in the lungs is possible. The effect is seen in rodents only at high doses. The clinical relevance of these findings is unknown.
Standard experiments with memantine have not shown genotoxicity. Lifetime studies in mice and rats have not revealed any evidence of carcinogenicity. Memantine was not teratogenic in rats and rabbits, even at maternally toxic doses, and no adverse effects on fertility were observed.
In rats, reduced fetal growth was observed at doses equivalent to or slightly higher than those administered to humans.

6. PHARMACEUTICAL PROPERTIES

6.1. List of excipients

Sorbitol
Colloidal silicon dioxide
Microcrystalline cellulose
Croscarmellose sodium
Sucralose

Crospovidone
Mint flavor
Magnesium stearate

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at room temperature below 25ºC and in a dry place.

6.5. The nature and content of the packaging

28 dispersible tablets are packaged in opaque PVC/PE/PVdC-Aluminum foil blister packs, in a cardboard box together with instructions for use.

6.6. Disposal of residues from the medicinal product for human use and other special measures

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

2022/218

9. FIRST REGISTRATION DATE/ REGISTRATION RENEWAL DATE

First registration date: 11.04.2022

Registration renewal date:

10. RENEWAL DATE OF SPC