

## SUMMARY OF PRIDUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

COGITO 10 MG FILM COATED TABLETS

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

#### Active substance:

Each tablet contains 8.31 mg of memantine equivalent to 10 mg of memantine hydrochloride.

#### Excipients:

176.25 mg of Bovine lactose monohydrate

For excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Film coated tablet.

They are almost white, oblong, biconvex, film-coated tablets with a score line on both sides. The purpose of the score line is to facilitate breaking the tablet into equal doses.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

COGITO® is used It is used in the treatment of moderate to severe Alzheimer's disease.

#### 4.2 Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's disease. Treatment should only be started if a caregiver is available who will regularly monitor the patient's drug intake. The diagnosis must be made in accordance with current guidelines. Tolerability and dosing of memantine should be assessed regularly, preferably within the first three months of treatment initiation.

Thereafter, the clinical benefit of memantine and the patient's tolerability should be reassessed regularly, in line with current clinical guidelines. Maintenance treatment can be continued as long as the therapeutic benefit is favorable and the patient tolerates the treatment well. If there is evidence that the therapeutic effect is no longer present, or if the patient does not tolerate the treatment, discontinuation of memantine should be considered.

#### Elderly:

##### Dose Titration

The recommended maximum daily dose is 20 mg per day. In order to reduce the risk of adverse effects, the maintenance dose should be reached gradually over the first three weeks, with weekly increments of 5 mg as follows:

**Week 1 (Days 1–7):** The patient should take half of a 10 mg film-coated tablet (i.e. 5 mg) once daily for 7 days.

**Week 2 (Days 8–14):** The patient should take one 10 mg film-coated tablet once daily for 7 days.

**Week 3 (Days 15–21):** The patient should take one and a half 10 mg film-coated tablets (i.e. 15 mg) once daily for 7 days.

**From Week 4 onwards:** The patient should take two 10 mg film-coated tablets (i.e. 20 mg) once daily.

### **Maintenance Dose**

The recommended maintenance dose is 20 mg per day.

### **Method of administration:**

COGITO® should be taken once daily, at the same time each day. The tablets can be taken with or without food.

### **Additional information on special populations:**

#### **Renal/Liver 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 should be 10 mg.

If the treatment is well tolerated for at least 7 days, and based on the standard titration schedule, the daily dose may be increased to 20 mg.

For patients with severe renal impairment (creatinine clearance 5–29 mL/min), the recommended dose is 10 mg per day.

### **Hepatic Impairment**

No dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh A and B).

There is no available data on the use of memantine in patients with severe hepatic impairment, therefore COGITO® is not recommended in these patients.

### **Pediatric Population**

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

### **Geriatric Population**

According to clinical studies, the recommended dose for patients aged 65 years and older is 20 mg per day, as described above (i.e. two 10 mg film-coated tablets once daily).

### **4.3 Contraindications**

Contraindicated in patients with hypersensitivity to the active substance or to any of the excipients

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

Caution is advised in patients with epilepsy, a history of convulsions, or a predisposition to epilepsy.

The concomitant use of NMDA antagonists such as amantadine, ketamine, or dextromethorphan should be avoided, as these compounds act on the same receptor system as memantine and may increase the risk of adverse effects, particularly those affecting the central nervous system (see section 4.5 “Interaction with other medicinal products and other forms of interaction”).

Patients should be monitored carefully in cases where factors that increase urinary pH are present (see section 5.2 “Elimination”).

These factors may include significant dietary changes (e.g., switching from a meat-based diet to a vegetarian diet) or the intensive intake of alkaline gastric buffers.

Urinary pH may also be increased in the presence of renal tubular acidosis (RTA) or severe urinary tract infections caused by *Proteus* bacteria.

In several clinical trials, patients with recent myocardial infarction, uncompensated congestive heart failure (NYHA Class III–IV), or uncontrolled hypertension were excluded. Therefore, due to limited available data, such patients should be closely monitored.

COGITO® 10 mg film-coated tablets contain lactose monohydrate of bovine origin as an excipient.

Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

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

Due to the pharmacological effects and mechanism of action of memantine, the following interactions may occur:

- Due to the mechanism of action of memantine, the following interactions may occur:
- The effects of L-dopa, dopaminergic agonists, and anticholinergics may be enhanced when co-administered with NMDA antagonists such as memantine.
- It may reduce the effects of barbiturates and neuroleptics.

- Co-administration of memantine with antispasmodic agents, dantrolene, or baclofen may modify their effects and require dose adjustments.
- Use of memantine in combination with amantadine should be avoided due to the risk of pharmacotoxic psychosis. Both substances are chemically related NMDA antagonists.
- The same precaution may apply to ketamine and dextromethorphan (see section 4.4 “Special warnings and precautions for use”).
- There is a published case report describing a possible risk associated with the combination of memantine and phenytoin.
- Other compounds that utilize the same renal cationic transport system as amantadine – such as cimetidine, ranitidine, procainamide, quinidine, quinine, and nicotine – may also interact with memantine and potentially increase plasma levels.
- When used concomitantly with hydrochlorothiazide (HCT) or any HCT-containing combinations, a reduction in HCT serum levels may occur.
- Post-marketing cases of elevated INR have been reported in patients receiving warfarin and memantine concomitantly. Although a causal relationship has not been established, close monitoring of prothrombin time or INR is advised in patients treated with oral anticoagulants.
- Clearance of memantine may be reduced when used with carbonic anhydrase inhibitors and sodium bicarbonate.

In single-dose pharmacokinetic studies in healthy young volunteers, no clinically relevant interactions were observed between memantine and either glyburide/metformin combination or donepezil.

In a clinical study conducted in healthy young volunteers, memantine had no effect on the pharmacokinetics of galantamine.

Memantine has not been found to inhibit CYP1A2, 2A6, 2C9, 2D6, 2E1, 3A, flavin-containing monooxygenases, epoxide hydrolase, or sulfation pathways in vitro.

#### **Additional information on special populations**

No interaction studies have been conducted.

#### **Pediatric population**

No interaction studies have been conducted.

## **4.6 Pregnancy and lactation**

### **General advice:**

Pregnancy category: C.

### **Women of childbearing potential/Contraception:**

There is no recommendation regarding the use of the drug in women of childbearing potential and those using contraception.

### **Pregnancy**

There is no clinical information available regarding the use of memantine during pregnancy.

Studies conducted in animals are insufficient with respect to effects on pregnancy, embryonal/fetal development, parturition, and/or postnatal development (see section 5.3).

The potential risk to humans is unknown. COGITO® should not be used during pregnancy unless clearly necessary.

### **Lactation**

There is no information regarding the excretion of memantine into human breast milk.

However, due to its lipophilic nature, it is likely to be excreted. Women using memantine should not breastfeed.

### **Fertility**

Animal studies indicate a reduction in intrauterine growth at exposure levels comparable to or slightly higher than those in humans (see section 5.3 Preclinical safety data).

## **4.7 Effects on ability to drive and use machines**

Moderate to severe Alzheimer's disease generally leads to a decline in driving performance and the ability to operate machinery. Additionally, memantine has a mild to moderate effect on the ability to drive and use machines. Therefore, patients receiving outpatient treatment should be advised to exercise caution.

## **4.8 Undesirable effects**

In clinical studies involving mild, moderate, and severe dementia, including 1,784 patients treated with memantine and 1,595 patients treated with placebo, the overall incidence of adverse events observed with memantine did not differ from that observed with placebo; adverse events were generally mild to moderate in severity. The most frequently reported adverse events with a higher incidence in the memantine group compared to placebo 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%).

The adverse drug reactions listed in the table below have been collected from memantine clinical trials and post-marketing experience. Within each frequency category, adverse

reactions are presented in order of decreasing severity. Adverse reactions are classified by system organ class according to the following frequency categories: 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 ( $<1/10,000$ ), and unknown (cannot be estimated from available data).

|                                                        |           |                                   |
|--------------------------------------------------------|-----------|-----------------------------------|
| Infections and infestations                            | Uncommon  | Fungal infections                 |
| Immune system disorders                                | Common    | Drug hypersensitivity             |
| Psychiatric disorders                                  | Common    | Drowsiness                        |
|                                                        | Uncommon  | Confusion                         |
|                                                        | Uncommon  | Hallucination <sup>1</sup>        |
|                                                        | Unknown   | Psychotic reactions <sup>2</sup>  |
| Nervous system disorders                               | Common    | Dizziness                         |
|                                                        | Common    | Balance disorders                 |
|                                                        | Uncommon  | Gait abnormality                  |
|                                                        | Very rare | Seizures                          |
| Cardiac disorders                                      | Uncommon  | Cardiac failure                   |
| Vascular disorders                                     | Common    | Hypertension                      |
|                                                        | Uncommon  | Venous thrombosis/thromboembolism |
| Respiratory system, thoracic and mediastinal disorders | Common    | Dyspnea                           |
| Gastrointestinal disorders                             | Common    | Constipation                      |
|                                                        | Uncommon  | Vomiting                          |
|                                                        | Unknown   | Pancreatitis <sup>2</sup>         |
| Hepatobiliary disorders                                | Common    | Increased liver function tests    |
|                                                        | Unknown   | Hepatitis                         |
| General disorders and administration site conditions   | Common    | Headache                          |
|                                                        | Uncommon  | Fatigue                           |

<sup>1</sup> Hallucinations have mostly been observed in patients with severe Alzheimer's disease.

<sup>2</sup> Isolated cases reported in post-marketing experience.

These events have been associated with Alzheimer's disease, depression, suicidal ideation, and suicide. Such cases have been reported in patients treated with memantine during post-marketing surveillance.

### Reporting of suspected adverse reactions

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.

## **4.9 Overdose and treatment**

Clinical experience with overdose is limited both in clinical trials and post-marketing phases. Symptoms:

Relatively large overdoses (e.g., 200 mg daily for 3 days and 105 mg daily) have been associated either only with symptoms such as fatigue, weakness, and/or diarrhea, or no symptoms at all. Patients who took less than 140 mg or an unknown dose showed symptoms related to the central nervous system (confusion, drowsiness, sudden sleep onset, vertigo, agitation, aggression, hallucinations, and gait disturbances) and/or gastrointestinal symptoms (vomiting and diarrhea).

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

In another major overdose case, a patient survived and recovered after orally taking 400 mg of memantine. This patient experienced CNS symptoms such as restlessness, psychosis, visual hallucinations, proconvulsiveness, drowsiness, 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 eliminate the drug, such as gastric lavage, activated charcoal (to prevent potential enterohepatic recirculation), urine acidification, and forced diuresis, should be applied as appropriate. If there are signs or symptoms of general central nervous system overstimulation, careful symptomatic clinical management should be considered.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic Group: Nervous System, Psychoanaleptics, Anti-dementia Drugs, Other Anti-dementia Drugs

ATC code: N06DX01

There is increasing evidence that dysfunction of glutamatergic neurotransmission at N-methyl-D-aspartate (NMDA) receptors contributes to the onset of symptoms and progression of neurodegenerative dementia.

Memantine is a voltage-dependent, moderate-affinity, non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist. It modulates the effects of pathologically elevated glutamate tonic levels that can lead to neuronal dysfunction and loss.

## **Clinical Studies**

A pivotal monotherapy study involving 252 outpatients with moderate to severe Alzheimer's disease (baseline MMSE total scores 3-14) demonstrated beneficial effects of memantine treatment compared to placebo over 6 months. Significant improvements were observed in the analysis of cases with the following endpoints:

CIBIC-plus (Clinician's Interview-Based Impression of Change):  $p=0.025$

ADCS-ADLsev (Alzheimer's Disease Cooperative Study – Activities of Daily Living, severe version):  $p=0.003$

SIB (Severe Impairment Battery):  $p=0.002$

In another pivotal monotherapy study including 403 patients with mild to moderate Alzheimer's disease (baseline MMSE total scores 10-22), patients treated with memantine showed statistically significant improvements compared to placebo at 24 weeks (LOCF analysis) in:

ADAS-cog (Alzheimer's Disease Assessment Scale-cognitive subscale):  $p=0.003$

CIBIC-plus:  $p=0.004$

A third monotherapy study randomized 470 patients with mild to moderate Alzheimer's disease (baseline MMSE scores 11-23). In the prospectively defined primary analysis at 24 weeks, no statistically significant effect was observed on the primary efficacy endpoint.

A meta-analysis of six phase III, placebo-controlled, 6-month trials in patients with moderate to severe Alzheimer's disease ( $MMSE < 20$ ), including both monotherapy studies and studies in patients on stable doses of acetylcholinesterase inhibitors, showed that memantine treatment produced statistically significant improvements in cognitive, global, and functional domains. When worsening in all three domains occurred simultaneously, results indicated that the rate of decline was approximately twice as high in placebo-treated patients compared to those treated with memantine, demonstrating a statistically significant disease-modifying effect of memantine (21% vs 11%,  $p < 0.0001$ ).

## **5.2 Pharmacokinetic properties**

### **General characteristics:**

#### **Absorption**

Memantine has an absolute bioavailability of approximately 100%. The  $T_{\text{max}}$  is 3 to 8 hours. Its absorption is not affected by food intake.

## **Distribution**

Daily doses of 20 mg result in steady-state plasma concentrations ranging between 70 and 150 ng/ml (0.5–1 µmol), with considerable interindividual variability. When administered at daily doses ranging from 5 to 30 mg, the average cerebrospinal fluid (CSF)/serum concentration ratio was approximately 0.52. The volume of distribution is about 10 l/kg. Approximately 45% of memantine is bound to plasma proteins.

## **Biotransformation**

In humans, about 80% of circulating memantine-related material exists as the parent compound. The primary metabolites in humans are N-3,5-dimethyl-gludantan, a mixture of 4- and 6-hydroxy-memantine isomers, and 1-nitroso-3,5-dimethyl-adamantane. None of these metabolites exhibit NMDA antagonist activity. In vitro studies did not detect metabolism catalyzed by cytochrome P450 enzymes. In a study using orally administered <sup>14</sup>C-memantine, approximately 84% of the dose was excreted within 20 days, with more than 99% eliminated renally.

## **Elimination**

Memantine exhibits mono-exponential elimination with a terminal half-life ( $t_{1/2}$ ) of 60 to 100 hours. In healthy volunteers with normal renal function, the total clearance ( $Cl_{tot}$ ) is approximately 170 ml/min/1.73 m<sup>2</sup>, with a portion of the total renal clearance attributed to tubular secretion. Renal clearance also involves tubular reabsorption, likely via cation transport proteins. Under alkaline urine conditions, memantine renal elimination can be reduced by a factor of 7–9 (see section 4.4 Special warnings and precautions for use). Urinary alkalinization can occur due to drastic dietary changes (e.g., switching from a meat-based to a vegetarian diet) or the substantial intake of alkaline gastric buffers.

## **Linearity**

Studies in volunteers have demonstrated linear pharmacokinetics in the 10–40 mg dose range.

## **Pharmacokinetic/Pharmacodynamic Relationship**

At a daily dose of 20 mg, CSF concentrations of memantine reach levels that correspond to the  $K_i$  value (inhibition constant) of approximately 0.5 µmol in the frontal cortex.

## **5.3 Preclinical safety data**

In short-term studies conducted in rats, memantine, like other NMDA antagonists, has been shown to cause neuronal vacuolization and necrosis (Olney lesions) only at doses that result in extremely high serum concentrations. Ataxia and other preclinical signs appeared prior to vacuolization and necrosis. These effects were not observed in long-term studies conducted in both rodents and non-rodents; therefore, the clinical relevance of these findings is unknown.

Ocular changes were observed in repeat-dose toxicity studies in rodents and dogs; however, these findings were not present in monkeys. Specific ophthalmologic examinations conducted during clinical studies with memantine did not reveal any ocular abnormalities.

Phospholipidosis in pulmonary macrophages, due to lysosomal accumulation of memantine, has been observed in rodents. This effect has also been noted with other cationic amphiphilic drugs. A correlation between this accumulation and vacuolization in the lungs is considered likely. These effects occurred in rodents only at high doses, and the clinical significance remains unclear.

Standard genotoxicity studies with memantine have not revealed any genotoxic potential. Lifetime carcinogenicity studies in mice and rats showed no evidence of carcinogenicity.

Even at maternally toxic doses, memantine demonstrated no teratogenic effects in rats and rabbits, and no adverse effects on fertility were observed. In rats, intrauterine growth retardation was noted at exposure levels equal to or slightly exceeding those used in humans.

## **6. PHARMACEUTICAL PROPERTIES**

### **6.1 List of excipients**

Lactose monohydrate (of bovine origin)

Microcrystalline cellulose

Colloidal silicon dioxide

Talc

Magnesium stearate

Titanium dioxide (E171)

Polyethylene glycol

Polyvinyl alcohol

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

36 months

### **6.4 Special storage precautions**

Store below 25°C at room temperature.

### **6.5 Nature and contents of the packaging**

Presented in PVC/PE/PVDC/Al foil blister packs containing 30, 50, or 100 film-coated tablets, together with the package leaflet, in a cardboard box.

### **6.6 Disposal of unused medicinal products and other special precautions**

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

**7. MARKETING AUTHORIZATION HOLDER**

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**8. MARKETING AUTHORIZATION NUMBER**

[To be completed nationally]

**9. INITIAL MARKETING AUTHORIZATION DATE / MARKETING  
AUTHORIZATION RENEWAL DATE**

[To be completed nationally]

**10. PACKAGE LEAFLET RENEWAL DATE**

[To be completed nationally]