

1 NAME OF THE MEDICINAL PRODUCT

Memantine Synthon 10 mg, tabletten

Memantine Synthon 20 mg, tabletten

Memantine Synthon 5 mg + 10 mg +15 mg + 20 mg, tabletten

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect: each tablet contains 144.32 mg lactose (as monohydrate).

Each 20 mg film-coated tablet contains 20 mg of memantine hydrochloride equivalent to 16.62 mg memantine.

Excipient(s) with known effect: each tablet contains 288.63 mg lactose (as monohydrate).

Each 5 mg film-coated tablet contains 5 mg of memantine hydrochloride equivalent to 4.15 mg memantine.

Excipient(s) with known effect: each tablet contains 72.16 mg lactose (as monohydrate).

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

Excipient(s) with known effect: each tablet contains 144.32 mg lactose (as monohydrate).

Each 15 mg film-coated tablet contains 15 mg of memantine hydrochloride equivalent to 12.46 mg memantine.

Excipient(s) with known effect: each tablet contains 216.48 mg lactose (as monohydrate).

Each 20 mg film-coated tablet contains 20 mg of memantine hydrochloride equivalent to 16.62 mg memantine.

Excipient(s) with known effect: each tablet contains 288.63 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White, film-coated, round (8 mm) biconvex tablets, scored with a wide pressure-sensitive division mark on one side and debossed with 'M9MN' and '10' on the other side.

The tablet can be divided into equal doses.

Pink, film-coated, oval (13.5 x 6.6 mm) biconvex tablets, scored with a wide pressure-sensitive division mark on one side and debossed with 'M9MN 20' on the other side.

The tablet can be divided into equal doses.

Yellow, film-coated, oval (8 x 4.5 mm) biconvex tablets, debossed with 'M9MN 5' on one side.

White, film-coated, round (8 mm) biconvex tablets, scored with a wide pressure-sensitive division mark on one side and debossed with 'M9MN' and '10' on the other side.

The tablet can be divided into equal doses.

Orange-brown, film-coated, round (9.3 mm) biconvex tablets, scored with a wide pressure-sensitive division mark on one side and debossed with 'M9MN 15' on the other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses

Pink, film-coated, oval (13.5 x 6.6 mm) biconvex tablets, scored with a wide pressure-sensitive division mark on one side and debossed with 'M9MN 20' on the other side.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adult patients with 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 dementia.

Posology

Therapy should only be started if a caregiver is available who will regularly monitor the intake of the medicinal product by the patient. Diagnosis should be made according to current guidelines. The tolerance and dosing of memantine should be reassessed on a regular basis, preferably within three months after start of treatment. Thereafter, the clinical benefit of memantine and the patient's tolerance of treatment should be reassessed on a regular basis according to current clinical guidelines. Maintenance treatment can be continued for as long as a therapeutic benefit is favourable and the patient tolerates treatment with memantine. Discontinuation of memantine should be considered when evidence of a therapeutic effect is no longer present or if the patient does not tolerate treatment.

Adults

Dose titration

~~<10 mg>~~ <20mg>

The maximum daily dose is 20 mg per day. In order to reduce the risk of undesirable effects the maintenance dose is achieved by upward titration of 5 mg per week over the first 3 weeks as follows:

Week 1 (day 1-7):

The patient should take half a 10 mg film-coated tablet (5 mg) per day for 7 days.

Week 2 (day 8-14):

The patient should take one 10 mg film-coated tablet per day for 7 days.

Week 3 (day 15-21):

The patient should take one and a half 10 mg film coated tablets (15 mg) per day for 7 days.

From Week 4 on:

The patient should take two 10 mg film-coated tablets (20 mg) or one 20 mg film-coated tablet per day.

Treatment Initiation Pack

Each pack contains 28 film-coated tablets in 4 blisters with 7 tablets of each strength.

The recommended starting dose is 5 mg per day, which is stepwise increased over the first 4 weeks of treatment reaching the recommended maintenance dose as follows:

Week 1 (day 1-7):

The patient should take one 5 mg film-coated tablet per day (yellow, oval biconvex) for 7 days.

Week 2 (day 8-14):

The patient should take one 10 mg film-coated tablet per day (white, round biconvex) for 7 days.

Week 3 (day 15-21):

The patient should take one 15 mg film-coated tablet per day (orange-brown, round biconvex) for 7 days.

Week 4 (day 22-28):

The patient should take one 20 mg film-coated tablet per day (pink, oval biconvex) for 7 days.

Maintenance dose

The recommended maintenance dose is 20 mg per day.

Elderly

On the basis of the clinical studies, the recommended dose for patients over the age of 65 years is 20 mg per day (two 10 mg film-coated tablets or one 20 mg film-coated tablet) as described above.

Renal impairment

In patients with mildly impaired renal function (creatinine clearance 50 – 80 ml/min) no dosage adjustment is required. In patients with moderate renal impairment (creatinine clearance 30 – 49 ml/min) daily dose should be 10 mg per day. If tolerated well after at least 7 days of treatment, the dose could be increased up to 20 mg/day according to standard titration scheme. In patients with severe renal impairment (creatinine clearance 5 – 29 ml/min) daily dose should be 10 mg per day.

Hepatic impairment

In patients with mild or moderate hepatic impaired function (Child-Pugh A and Child-Pugh B), no dose adjustment is needed. No data on the use of memantine in patients with severe hepatic impairment are available. Administration of Memantine Syntho is not recommended in patients with severe hepatic impairment.

Paediatric population

No data available.

Method of administration

Memantine Synthon should be administered orally once a day and should be taken at the same time every day. The film-coated tablets can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Caution is recommended in patients with epilepsy, former history of convulsions or patients with predisposing factors for epilepsy.

Concomitant use of N-methyl-D-aspartate (NMDA)-antagonists such as amantadine, ketamine or dextromethorphan should be avoided. These compounds act at the same receptor system as memantine, and therefore adverse reactions (mainly central nervous system (CNS)-related) may be more frequent or more pronounced (see also section 4.5).

Some factors that may raise urine pH (see section 5.2 “Elimination”) may necessitate careful monitoring of the patient. These factors include drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or a massive ingestion of alkalisating gastric buffers. Also, urine pH may be elevated by states of renal tubular acidosis (RTA) or severe infections of the urinary tract with *Proteus* bacteria.

In most clinical trials, patients with recent myocardial infarction, uncompensated congestive heart failure (NYHA III-IV), or uncontrolled hypertension were excluded. As a consequence, only limited data are available and patients with these conditions should be closely supervised.

Lactose intolerance

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

- The mode of action suggests that the effects of L-dopa, dopaminergic agonists, and anticholinergics may be enhanced by concomitant treatment with NMDA-antagonists such as memantine. The effects of barbiturates and neuroleptics may be reduced. Concomitant administration of memantine with the antispasmodic agents, dantrolene or baclofen, can modify their effects and a dose adjustment may be necessary.
- Concomitant use of memantine and amantadine should be avoided, owing to the risk of pharmacotoxic psychosis. Both compounds are chemically related NMDA-antagonists. The same

may be true for ketamine and dextromethorphan (see also section 4.4). There is one published case report on a possible risk also for the combination of memantine and phenytoin.

- Other active substances such as cimetidine, ranitidine, procainamide, quinidine, quinine and nicotine that use the same renal cationic transport system as amantadine may also possibly interact with memantine leading to a potential risk of increased plasma levels.
- There may be a possibility of reduced serum level of hydrochlorothiazide (HCT) when memantine is co-administered with HCT or any combination with HCT.
- In post-marketing experience isolated cases with international normalized ratio (INR) increases have been reported in patients concomitantly treated with warfarin. Although no causal relationship has been established, close monitoring of prothrombin time or INR is advisable for patients concomitantly treated with oral anticoagulants.

In single dose pharmacokinetic (PK) studies in young healthy subjects no relevant active substance-active substance interaction of memantine with glyburide/metformin or donepezil was observed.

In a clinical study in young healthy subjects no relevant effect of memantine on the pharmacokinetics of galantamine was observed.

Memantine did not inhibit CYP 1A2, 2A6, 2C9, 2D6, 2E1, 3A, flavin-containing monooxygenase, epoxide hydrolase or sulphation *in vitro*.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of memantine in pregnant women. Animal studies indicate a potential for reducing intrauterine growth at exposure levels, which are identical or slightly higher than at human exposure (see section 5.3). The potential risk for humans is unknown. Memantine should not be used during pregnancy unless clearly necessary.

Breast-feeding

It is not known whether memantine is excreted in human breast milk but, taking into consideration the lipophilicity of the substance, this probably occurs. Women taking memantine should not breast-feed.

Fertility

No adverse reactions of memantine were noted on male and female fertility.

4.7 Effects on ability to drive and use machines

Moderate to severe Alzheimer's disease usually causes impairment of driving performance and compromises the ability to use machinery. Furthermore, Memantine Synthon has minor or moderate influence on the ability to drive and use machines such that outpatients should be warned to take special care.

4.8 Undesirable effects

Summary of the safety profile

In clinical trials in mild to severe dementia, involving 1,784 patients treated with memantine and 1,595 patients treated with placebo, the overall incidence rate of adverse reactions with memantine did not differ from those with placebo; the adverse events were usually mild to moderate in severity. The most frequently occurring adverse events with a higher incidence in the memantine group than in the placebo group were dizziness (6.3% vs 5.6%, respectively), 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%).

Tabulated list of adverse reactions

The following Adverse Drug Reactions listed in the Table below have been accumulated in clinical studies with memantine and since its introduction in the market.

Adverse reactions are ranked according to system organ class, using the following convention: 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). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Infections and infestations	Uncommon	Fungal infections
Immune system disorders	Common	Drug hypersensitivity
Psychiatric disorders	Common	Somnolence
	Uncommon	Confusion
	Uncommon	Hallucinations ¹
	Not known	Psychotic reactions ²
Nervous system disorders	Common	Dizziness
	Common	Balance disorder
	Uncommon	Gait abnormal
	Very rare	Seizures
Cardiac disorders	Uncommon	Cardiac failure
Vascular disorders	Common	Hypertension
	Uncommon	Venous thrombosis/thromboembolism
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea

Gastrointestinal disorders	Common	Constipation
	Uncommon	Vomiting
	Not known	Pancreatitis ²
Hepatobiliary disorders	Common	Elevated liver function test
	Not known	Hepatitis
General disorders and administration site conditions	Common	Headache
	Uncommon	Fatigue

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

²Isolated cases reported in post-marketing experience.

Alzheimer's disease has been associated with depression, suicidal ideation and suicide. In post-marketing experience these reactions have been reported in patients treated with Memantine.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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
Nederlands Bijwerkingen Centrum Lareb
Website: www.lareb.nl

4.9 Overdose

Only limited experience with overdose is available from clinical studies and post-marketing experience.

Symptoms

Relative large overdoses (200 mg and 105 mg/day for 3 days, respectively) have been associated with either only symptoms of tiredness, weakness and/or diarrhoea or no symptoms. In the overdose cases below 140 mg or unknown dose the patients revealed symptoms from central nervous system (confusion, drowsiness, somnolence, vertigo, agitation, aggression, hallucination, and gait disturbance) and/or of gastrointestinal origin (vomiting and diarrhoea).

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

In another case of a large overdose, the patient also survived and recovered. The patient had received 400 mg memantine orally. The patient experienced central nervous system symptoms such as restlessness, psychosis, visual hallucinations, proconvulsiveness, somnolence, stupor, and unconsciousness.

Treatment

In the event of overdose, treatment should be symptomatic. No specific antidote for intoxication or overdose is available. Standard clinical procedures to remove active substance material, e.g. gastric lavage, carbo medicinalis (interruption of potential entero-hepatic recirculation), acidification of urine, forced diuresis should be used as appropriate.

In case of signs and symptoms of general CNS overstimulation, careful symptomatic clinical treatment should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychoanaleptics; other Anti-dementia drugs.

ATC code: N06DX01

There is increasing evidence that malfunctioning of glutamatergic neurotransmission, in particular at NMDA-receptors, contributes to both expression of symptoms and disease progression in neurodegenerative dementia.

Memantine is a voltage-dependent, moderate-affinity uncompetitive NMDA-receptor antagonist. It modulates the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction.

Clinical studies

A pivotal monotherapy study in a population of patients suffering from moderate to severe Alzheimer's disease (mini mental state examination (MMSE) total scores at baseline of 3 - 14) included a total of 252 outpatients. The study showed beneficial effects of memantine treatment in comparison to placebo at 6 months (observed cases analysis for the clinician's interview based impression of change (CIBIC-plus): $p=0.025$; Alzheimer's disease cooperative study – activities of daily living (ADCS-ADLsev): $p=0.003$; severe impairment battery (SIB): $p=0.002$).

A pivotal monotherapy study of memantine in the treatment of mild to moderate Alzheimer's disease (MMSE total scores at baseline of 10 to 22) included 403 patients. Memantine-treated patients showed a statistically significantly better effect than placebo-treated patients on the primary endpoints: Alzheimer's disease assessment scale (ADAS-cog) ($p=0.003$) and CIBIC-plus ($p=0.004$) at week 24 (last observation carried forward (LOCF)).

In another monotherapy study in mild to moderate Alzheimer's disease a total of 470 patients (MMSE total scores at baseline of 11-23) were randomised. In the prospectively defined primary analysis statistical significance was not reached at the primary efficacy endpoint at week 24.

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

as twice as many placebo-treated patients as memantine-treated patients showed worsening in all three domains (21% vs. 11%, $p < 0.0001$).

5.2 Pharmacokinetic properties

Absorption

Memantine has an absolute bioavailability of approximately 100%. T_{max} is between 3 and 8 hours. There is no indication that food influences the absorption of memantine.

Distribution

Daily doses of 20 mg lead to steady-state plasma concentrations of memantine ranging from 70 to 150 ng/ml (0.5 - 1 μ mol) with large interindividual variations. When daily doses of 5 to 30 mg were administered, a mean cerebrospinal fluid (CSF)/serum ratio of 0.52 was calculated. The volume of distribution is around 10 l/kg. About 45% of memantine is bound to plasma-proteins.

Biotransformation

In man, about 80% of the circulating memantine-related material is present as the parent compound. Main human metabolites are N-3,5-dimethyl-gludantan, the isomeric mixture of 4- and 6-hydroxymemantine, and 1-nitroso-3,5-dimethyl-adamantane. None of these metabolites exhibit NMDA-antagonistic activity. No cytochrome P 450 catalysed metabolism has been detected *in vitro*.

In a study using orally administered 14 C-memantine, a mean of 84% of the dose was recovered within 20 days, more than 99% being excreted renally.

Elimination

Memantine is eliminated in a monoexponential manner with a terminal $t_{1/2}$ of 60 to 100 hours. In volunteers with normal kidney function, total clearance (Cl_{tot}) amounts to 170 ml/min/1.73 m² and part of total renal clearance is achieved by tubular secretion.

Renal handling also involves tubular reabsorption, probably mediated by cation transport proteins. The renal elimination rate of memantine under alkaline urine conditions may be reduced by a factor of 7 to 9 (see section 4.4). Alkalisiation of urine may result from drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or from the massive ingestion of alkalisating gastric buffers.

Linearity

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

Pharmacokinetic/pharmacodynamic relationship

At a dose of memantine of 20 mg per day the CSF levels match the k_i -value (k_i = inhibition constant) of memantine, which is 0.5 μ mol in human frontal cortex.

5.3 Preclinical safety data

In short term studies in rats memantine like other NMDA-antagonists have induced neuronal vacuolisation and necrosis (Olney lesions) only after doses leading to very high peak serum concentrations. Ataxia and other preclinical signs have preceded the vacuolisation and necrosis. As the effects have neither been observed in long term studies in rodents nor in non-rodents, the clinical relevance of these findings is unknown.

Ocular changes were inconsistently observed in repeat dose toxicity studies in rodents and dogs, but not in monkeys. Specific ophthalmoscopic examinations in clinical studies with memantine did not disclose any ocular changes.

Phospholipidosis in pulmonary macrophages due to accumulation of memantine in lysosomes was observed in rodents. This effect is known from other active substances with cationic amphiphilic properties. There is a possible relationship between this accumulation and the vacuolisation observed in lungs. This effect was only observed at high doses in rodents. The clinical relevance of these findings is unknown.

No genotoxicity has been observed following testing of memantine in standard assays. There was no evidence of any carcinogenicity in life long studies in mice and rats. Memantine was not teratogenic in rats and rabbits, even at maternally toxic doses, and no adverse effects of memantine were noted on fertility. In rats, foetal growth reduction was noted at exposure levels, which are identical or slightly higher than at human exposure.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Cellulose, microcrystalline
Talc
Silica, Colloidal Anhydrous
Magnesium stearate

Tablet coating

Lactose monohydrate
Hypromellose
Titanium dioxide (E171)
Macrogol 4000
Iron oxide yellow (E172) <5, 15, 20 mg>
Iron oxide red (E172) <15, 20 mg>

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.

6.5 Nature and contents of container

PVC/Al blister packs

For 10 mg strength:

blisters containing 10, 14, 20, 28, 30, 42, 50, 56, 60, 90, 98, 100, 112 or 120 tablets and a Unit dose blister containing 30x1 tablet

Not all pack sizes may be marketed.

For 20 mg strength:

blisters containing 10, 14, 20, 28, 30, 42, 50, 56, 60, 90, 98, 100, 112 or 120 tablets and a Unit dose blister containing 30x1 tablet

Not all pack sizes may be marketed.

Treatment initiation pack: 7x5 mg; 7x10 mg; 7x15 mg; 7x20 mg

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Synthon BV
Microweg 22
6545 CM Nijmegen
Nederland

8 MARKETING AUTHORISATION NUMBER(S)

RVG 112097
RVG 112098
RVG 112099

9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 17 oktober 2013

Datum van laatste verlenging: 12 september 2018

10 DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubrieken 4.1, 4.2, 4.4, 4.6, 4.7, 4.8 en 5.1; 29 september 2018.