EXENTA

10 mg film-coated tablets
Memantine hydrochloride

1.NAME OF THE MEDICINAL PRODUCT

Exenta®10 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of memantine hydrochloride (equivalent to 8.31 mg memantine).
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.
Description of tablets: White, peanut-shaped film-coated scored tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Exenta® is indicated for the treatment of 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. Therapy should only be started if a caregiver is available who will regularly monitor drug intake by the patient.

Adults: The recommended daily dose is 20 mg per day. In order to reduce the risk of side effects the maintenance dose is achieved by upward titration 5 mg per week over the first 3 weeks as follows:
Treatment should be started with 5 mg daily (half a tablet in the morning) during the 1st week. In the 2nd week, 10 mg per day (half a tablet twice a day) and in the 3rd week, 15 mg per day is recommended (one tablet in the morning and half a tablet in the afternoon). From the 4th week on, treatment can be continued with the recommended maintenance dose of 20 mg per day (one tablet twice a day).
The tablets can be taken with or without food.

Elderly: On the basis of the clinical studies the recommended dose for patients over the age of 65 years is 20 mg per day (10 mg twice a day) as described above.

Children and adolescents under the age of 18 years: The safety and efficacy of memantine in children and adolescents have not been established.

Renal impairment: In patients with normal to mildly impaired renal function (creatinine clearance 50 - 80 ml/min) no dose reduction is needed. In patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) daily dose should be reduced to 10 mg per day. A dose of 5 mg BID is recommended in patients with severe renal impairment (creatinine clearance of 5 - 29 ml/min) (see sections 4.4 and 5.2).

Hepatic impairment: Memantine HCl undergoes partial hepatic metabolism, with about 48% of administered dose excreted in urine as unchanged drug. No dosage adjustment is needed in patients with mild or moderate hepatic impairment. Memantine should be administered with caution to patients with severe hepatic impairment.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and special precautions for use

A dosage reduction is recommended in patients with severe renal impairment.
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 drug reactions (mainly 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 alkalising gastric buffers. Also, urine pH may be elevated by states of renal tubulary 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), and uncontrolled hypertension were excluded. As a consequence, only limited data are available and patients with these conditions should be closely supervised.

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 dosage 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 drugs 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 excretion of hydrochlorothiazide (HCT) when memantine is co-administered with HCT or any combination with HCT.
- In post marketing experience, isolated cases with 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.
Memantine did not inhibit CYP 1A2, 2A6, 2C9, 2D6, 2E1, 3A4, flavin containing monoxygenase, epoxide hydrolase and sulphation in vitro.

4.6 Pregnancy and lactation

Pregnancy: For memantine, no clinical data on exposed pregnancies are available.
Animal studies indicate a potential for reducing intrauterine growth at exposure levels which are 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.

Lactation: It is not known whether memantine is excreted in humans' breast milk; caution should be exercised when memantine is administered to a nursing mother.

4.7 Effects on ability to drive and use machines

Moderately severe to severe Alzheimer's disease usually causes impairment of driving performance and compromises the ability to use machinery. Furthermore, memantine may change reactivity such that outpatients should be warned to take special care when driving a vehicle or operating machinery.

4.8 Undesirable effects

In clinical trials in mild to severe dementia, involving 1784 patients treated with memantine and 1595 patients treated with placebo, the overall incidence rate of adverse events 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%).
The following Adverse Drug Reactions listed 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to ≤1/100), rare (≥1/10,000 to ≤1/1,000), very rare (≤1/10,000), not known (cannot be estimated from the available data).

Body as a whole - general disorders:
Common: Headache
Uncommon: Fatigue

Psychiatric disorders:
Common: Somnolence
Uncommon: Confusion and hallucinations *
Not known: Psychotic reactions **

Gastro-intestinal system disorders:
Common: Constipation
Uncommon: Vomiting
Not known: Pancreatitis **

Central & Peripheral nervous system disorders:
Common: Dizziness
Uncommon: Gait abnormal
Very rare: Seizures

Alzheimer's disease has been associated with

* Hallucinations have mainly been observed in patients with severe Alzheimer's disease.
** Isolated cases reported in post-marketing experience.

depression, suicidal ideation and suicide. In post-marketing experience these events have been reported in patients treated with memantine.

4.9 Overdose
There have been very few cases of overdose. Over dosage affects the central nervous system (restlessness, psychosis, visual hallucinations, proconvulsiveness, somnolence, stupor and unconsciousness); symptoms resolved without permanent sequelae. The largest known ingestion of memantine worldwide was 2.0 grams. Treatment of overdosage should be symptomatic. Elimination of memantine can be enhanced by acidification of urine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group:
Antidementia drugs, ATC code: N06DX01.
Persistent activation of central nervous system N-methyl-D-aspartate (NMDA) receptors by the excitatory amino acid glutamate has been hypothesized to contribute to the symptomatology of Alzheimer's disease. Memantine is a voltage-dependent, moderate-affinity uncompetitive NMDA-receptor antagonist. It modulates the effects of pathologically elevated 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 (MMSE [Mini-Mental State Examination] 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 CIBIC-plus (Clinician's Interview-Based Impression of Change Plus Caregiver Input): p = 0.025; ADCS-ADLsev [Alzheimer's Disease Cooperative Study - Activities of Daily Living inventory]:p = 0.003; SIB [Severe Impairment Battery]: 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: ADAS-cog (Alzheimer Disease Assessment Scale Cognitive) (p = 0.003) and CIBIC-plus (p = 0.004) at week 24 (LOCF [Last study Observation Carried Forward]). 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%. Peak concentration is reached between 3 and 8 hours. There is no indication that food influences the absorption of memantine.

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

Distribution: Daily doses of 20 mg lead to steady state plasma concentrations of memantine ranging from 70 to 150 ng/ml (0.5 - 1 µmol) with large inter-individual variations. When daily doses of 5 to 30 mg were administered, a mean CSF/serum ratio of 0.52 was calculated [CSF: Cerebrospinal fluid]. 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 is present as the parent compound. Main human metabolites are N-3,5-dimethylgludantan, the isomeric mixture of 4- and 6-hydroxy-memantine 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 (Cltot) amounts to 170 ml/min/1.73 m^2 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). Alkalisation of urine may result from drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or from the massive ingestion of alkalinizing gastric buffers.

Specific patient population:
In elderly volunteers with normal and reduced renal function (creatinine clearance of 50 - 100 ml/min), a significant correlation was observed between creatinine clearance and total renal clearance of memantine (see section 4.2).
The effect of liver disease on the pharmacokinetics of memantine has not been studied. As memantine is metabolised to a minor extent only, and into metabolites with no NMDA antagonistic activity, clinically relevant changes in the pharmacokinetics are not expected in mild to moderate liver impairment.

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

5.3 Preclinical safety data
In short-term studies in rats, memantine like other NMDA antagonists has induced neuronal vacuolization and necrosis (Olney lesions) only after doses leading to very high peak serum concentrations.
Ataxia and other preclinical signs have preceded the vacuolization 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.
Phospholipidosis in pulmonary macrophages due to accumulation of memantine in lysosomes was observed in rodents. This effect is known from other drugs with cationic amphiphilic properties. There is a possible relationship between this accumulation and the vacuolization 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; Microcrystalline cellulose; Colloidal anhydrous silica; Talc; Magnesium stearate.
Tablet coat:
Lecithin; Polyethylene glycol; Polyvinyl alcohol; Talc and titanium dioxyde.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Do not store above 30ºC.
Store in the original package.

6.5 Nature and contents of container
Available in blister packs of 30 tablets.

Keep out of reach and sight of children.

Do not use after expiry date.

This is a Medicament

-Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
-Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
-The doctor and the pharmacist are the experts in medicines, their benefits and risks.
-Do not by yourself interrupt the period of treatment prescribed for you.
-Do not repeat the same prescription without consulting your doctor
-Keep all medicaments out of reach of children

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