Proposed Prescribing Information
For the use of a Registered Medical Practitioner or a Hospital or a Laboratory

MEMENTOR TABLETS 20 MG
MEMANTINE HYDROCHLORIDE TABLETS

BRAND OR PRODUCT NAME
MEMENTOR TABLETS 20 MG

NAME AND STRENGTH OF ACTIVE SUBSTANCE(S)
Each film coated tablet contains:
20 mg Memantine Hydrochloride equivalent to 16.62 mg Memantine
Colours: Titanium Dioxide, Yellow Oxide of Iron & Red Oxide of Iron

PRODUCT DESCRIPTION
Pale red to grey red colored, oval shaped, biconvex, bevel edged, film coated tablets, debossed '20' on one side and plain on other side.

DOSAGE FORM
Film coated tablet

PHARMACODYNAMICS / PHARMACOKINETICS
Pharmacodynamics
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.

Pharmacokinetics
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 µmol) with large inter-individual 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: It is reported that 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-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 reported *in vitro.*

Elimination: Memantine is eliminated in a mono-exponential manner with a terminal $t_{½}$ of 60 to 100 hours. 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. 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 alkalising gastric buffers.

Linearity: 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 cerebrospinal fluid (CSF) levels match the k_i-value (k_i = inhibition constant) of memantine, which is 0.5 µmol in human frontal cortex.

INDICATION
Treatment of patients with moderate to severe Alzheimer's disease

RECOMMENDED DOSAGE AND MODE 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 the intake of the medicinal product by the patient. Diagnosis should be made according to current guidelines.
Memantine should be administered once a day and should be taken at the same time every day. The tablets can be taken with or without food.

Route of administration: Oral

Adults:
Dose titration
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 5 mg per day For 7 days.

Week 2 (day 8-14):
The patient should take one 10 mg per day for 7 days.

Week 3 (day 15-21):
The patient should take 15 mg per day for 7 days.

From Week 4 on:
The patient should take 20 mg per day.

Maintenance dose:
The recommended maintenance dose is 20 mg per day.

Elderly: The recommended dose for Patients over the age of 65 years is 20 mg per day (or two

10 mg tablets once a day) as described above.

Children and adolescents: Memantine is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.

Renal impairment: In patients with mildly impaired renal function- (Creatinine Clearance 50-80 ml/min) no dose 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 reported. Administration of Memantine is not recommended in patients with severe hepatic impairment.

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

WARNINGS AND PRECAUTIONS
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 frequent or more pronounced.

Some factors that may raise urine pH 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*.

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

INTERACTIONS WITH OTHER MEDICAMENTS
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. Reported information also reflects possible risk 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.
- Isolated cases with international normalization ratio (INR) increases have been reported in patients concomitantly treated with warfarin. Although no causal relationship has been reported, 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, 3A, flavin-containing monooxygenase, epoxide hydrolase or sulphation *in vitro*.

STATEMENT ON USAGE DURING PREGNANCY AND LACTATION

Pregnancy

For memantine, no clinical data on exposed pregnancies are reported. Animal studies reported a potential for reducing intrauterine growth at exposure levels, which are identical or slightly higher than at human exposure. 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 human breast milk but, taking into consideration the lipophilicity of the substance, this probably occurs. Women taking memantine should not breast-feed.

ADVERSE EFFECTS / UNDESIRABLE EFFECTS

Following adverse events has been reported with use of memantine:
Cardiac disorders: Cardiac failure
Nervous system disorder: Dizziness, Gait abnormal, Seizures
Gastrointestinal disorders: Constipation, Vomiting, pacreatitis
Infections and infestations: Fungal infections
Vascular disorders: Hypertension, Venous thrombosis/thromboembolism
General disorders and administration site conditions: Headache, Fatigue
Psychiatric disorders: Somnolence, Confusion, Hallucinations (Hallucinations have mainly been reported in patients with severe Alzheimer’s disease), Psychotic reactions.

Alzheimer's disease has been associated with depression, suicidal ideation and suicide. These events have been reported in patients treated with Memantine.

OVERDOSE AND TREATMENT

Symptoms: Relatively 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 overdosage, 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 overdosage, 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 over-stimulation, careful symptomatic clinical treatment should be considered.

STORAGE CONDITIONS

Store below 30° C

PACKAGING AVAILABLE

Mementor Tablets are packed in Alu PVC/PVDC blister of 10 tablets. Such blisters containing 10 Tablets are packed into boxes of 10's, 30's, 60's and 100's. Not all presentations or all pack sizes may be marketed.

DATE OF REVISION OF PACKAGE INSERT

26/04/2016

NAME AND ADDRESS OF MANUFACTURER

TORRENT PHARMACEUTICALS LTD.
Indrad 382 721, District: Mehsana
INDIA.