For the use of a Registered Medical Practitioner or a Hospital or a Laboratory

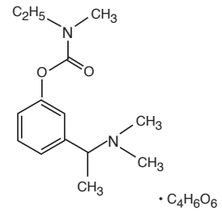
xxxxxxxx-5253

RIVADEM 1.5 MG CAPSULE
RIVADEM 3 MG CAPSULE
RIVADEM 4.5 MG CAPSULE
RIVADEM 6 MG CAPSULE

(Rivastigmine Capsules, 1.5/3.0/4.5/6.0 mg)

COMPOSITION:
Each hard gelatin capsule contains:
Rivastigmine Hydrogen Tartrate equivalent to Rivastigmine ..... 1.5 mg
Rivastigmine Hydrogen Tartrate equivalent to Rivastigmine .....3.0 mg
Rivastigmine Hydrogen Tartrate equivalent to Rivastigmine ..... 4.5 mg
Rivastigmine Hydrogen Tartrate equivalent to Rivastigmine .....6.0 mg

DESCRIPTION:
Rivadem Capsules (rivastigmine tartrate) is a reversible cholinesterase inhibitor and is known chemically as (S)-N-Ethyl-N-methyl-3-[1-(dimethylamino)ethyl]-phenyl carbamate hydrogen-(2R,3R)-tartrate. It has an empirical formula of $C_{14}H_{22}N_2O_2 \cdot C_4H_6O_6$ (hydrogen tartrate salt) and a molecular weight of 400.42 Rivastigmine tartrate is a white to off-white, fine crystalline powder that is very soluble in water, soluble in ethanol and acetonitrile, slightly soluble in n-octanol and very slightly soluble in ethyl acetate. The distribution coefficient at 37°C in n-octanol/phosphate buffer solution pH 7 is 3.0. The structural formula of rivastigmine is:



Rivadem Capsules Capsules contain rivastigmine tartrate, equivalent to 1.5, 3.0, 4.5 and 6.0 mg of rivastigmine base for oral administration

PHARMACOLOGICAL ACTION:
Pathological changes in Dementia of the Alzheimer type involve cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. These pathways are thought to be intricately involved in memory, attention, learning, and other cognitive processes. While the precise mechanism of rivastigmine's action is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. If this proposed mechanism is correct, Rivadem Capsules's effect may lessen as the disease process advances and fewer Cholinergic neurons remain functionally intact. There is no evidence that rivastigmine alters the course of the underlying dementing process. After a 6-mg dose of rivastigmine, anticholinesterase activity is present in CSF for about 10 hours, with a maximum inhibition of about 60% five hours after dosing. In vitro and in vivo studies demonstrate that the inhibition of cholinesterase by rivastigmine is not affected by the concomitant administration of memantine, an N-methyl-D-aspartate receptor antagonist.

Pharmacokinetics:
Absorption: Rivastigmine is well absorbed after oral administration. Oral absolute bioavailability is about 40%. Linear pharmacokinetics up to 6 mg in divided doses has been established. Doubling the dose from 3 to 6 mg BID results in a 4.4-fold increase in AUC. Peak plasma concentrations (Cmax) are achieved at 1.3 & 2.07 hrs after administration of 3 & 6mg dose respectively. Mean maximum plasma concentrations were found to be 5128.376pg/ml & 13022.722 pg/ml for 3 & 6mg dose respectively when administered orally. Rivastigmine absorption is delayed by food.
Distribution: Rivastigmine is widely distributed throughout the body with a volume of distribution in the range of 1.8-2.7 L/kg. Rivastigmine penetrates the blood brain barrier, reaching CSF peak concentrations in 1.4-2.6 hours. Mean AUC 1-12hr ratio of CSF/plasma averaged 40 ± 0.5% following 1-6 mg BID doses. Rivastigmine is about 40% bound to plasma proteins at concentrations of 1-400 ng/mL, which cover the therapeutic concentration range.
Metabolism: Rivastigmine is rapidly and extensively metabolized, primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite. No drug interaction related to Cytochrome P450 has been reported in humans.
Elimination:
The major pathway of elimination is via kidneys. Mean plasma half life of Rivastigmine in adult are 1.2 & 1.4hrs following oral administration of 3 & 6mg doses. Mean residence time of Rivastigmine is 2.4hrs for 3mg dose & 3.5hrs after administration of 6mg dose.
Special Populations:-
Hepatic Disease: Dosage adjustment is not required in hepatically impaired patients as the dose of drug is individually titrated to tolerability.
Renal Disease: Dosage adjustment may not be required in renally impaired patients as the dose of the drug is individually titrated to tolerability.
Age: mean oral clearance of Rivastigmine was reported to be lower in elderly than in younger subjects.
Gender and Race: It has been reported that gender & race did not affect the clearance of Rivastigmine.
Nicotine Use: It has been reported that nicotine use increases the oral clearance of Rivastigmine.

INDICATIONS:
Rivadem Capsules (Rivastigmine Capsules) is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

CONTRA-INDICATIONS:
Rivadem Capsules (Rivastigmine Capsules) is contraindicated in patients with known hypersensitivity to rivastigmine, other carbamate derivatives or other inactive ingredients of the preparation.
Rivastigmine is contra-indicated in patient with sever liver impairment since it has not been studied in this population.

WARNING AND PRECAUTIONS
The incidence and severity of adverse events generally increase with higher doses. If treatment is interrupted for more than several days, it should be re-initiated at 1.5 mg twice daily to reduce the possibility of adverse reactions (e.g. vomiting).
Dose titration: Adverse effects (e.g. hypertension, hallucinations) have been observed shortly after dose increase. They may respond to a dose reduction. In other cases rivastigmine has been discontinued.
Gastrointestinal disorder such as nausea and vomiting may particularly when initiating treatment and/or Increasing the dose. The adverse event occurs more commonly in women. Patients with Alzheimer's disease may lose weight. Cholinesterase inhibitors, including rivastigmine have been associated with weight loss in these patients. During therapy patient's weight should be monitored. As with other cholinomimetics, care must be taken when using rivastigmine in patients with sick sinus syndrome or conduction defects (sino atrial blocks, atrioventricular block) As with other cholinergic substances, rivastigmine may cause increased gastric acid secretions. Care should be exercised in treating patients with active gastric or duodenal ulcers or patients predisposed to these conditions. Cholinesterase inhibitors should be prescribed with care to patients with history of asthma or obstructive pulmonary disease.
Cholinomimetics may induce or exacerbate urinary obstruction and seizures.
Caution is recommended in treating patients predisposed to such diseases.
The uses of rivastigmine in patients with severe Alzheimer's dementia, other types of dementia or other types of memory impairment (e.g. age related cognitive decline) has not been investigated.
Like other cholinomimetics, rivastigmine may exacerbate or induce extrapyramidal symptoms, including worsening in patients with Parkinson's disease.

Q T Prolongation and torsade de pointes :
Electrocardiogram QT prolongation may occur in patients treated with certain cholinesterase inhibitor products including rivastigmine. Rivastigmine may cause bradycardia which constitutes a risk factor in the occurrence of torsade de pointes, predominantly in patients with risk factors. Caution is advised in patients at higher risk of developing torsade de pointes; for example, those with uncompensated heart failure, recent myocardial infarction, bradyarrhythmias, hypokalemia or hypomagnesemia, personal or family history of QT prolongation, or concomitant use with medicinal products known to induce QT prolongation and/or torsade de pointes. Clinical monitoring may also be required.

DRUG INTERACTION
As a cholinesterase inhibitor, rivastigmine may exaggerate the effect of succinylcholine-type muscle relaxants during anaesthesia. In view of its pharmacodynamic effects, rivastigmine should not be given concomitantly with others cholinomimetic drugs and might interfere with the activity of anticholinergic medications.
No pharmacokinetics interaction was observed between rivastigmine and digoxin, warfarin, diazepam or fluoxetine in studies in healthy volunteers. The increase in prothrombin time induced by warfarin is not affected by administration of rivastigmine. No untoward effects on cardiac conduction were observed following concomitant administration of digoxin and rivastigmine.
According to its metabolism, metabolic drug interactions appears unlikely, although rivastigmine may inhibit the butyrylcholinesterase mediated metabolism of other drugs.

Medicinal products known to prolong the QT interval :
Caution is advised when rivastigmine is used in combination with other medicinal products known to prolong the OT interval (including but not limited to quinidine, amiodarone, pimozide, halofantrine, cisapride, citalopram, mizolastin, moxifloxacin, erythromycin). Clinical monitoring may also be required.

PREGNACY AND LACTATION
Pregnancy: No clinical data on exposed pregnancies are available. No effects on fertility or embryofoetal development were observed in rat and rabbits, except at doses related to maternal toxicity. In peri/postnatal studies in rats, an increased gestation time was observed. Rivastigmine should not be used during pregnancy unless clearly necessary.
Lactation: In animal Rivastigmine is excreted into milk. It is not known if Rivastigmine is excreted into human milk. Therefore, Women on Rivastigmine should not breast-feed.

DOSAGE AND DIRECTIONS FOR USE:
The starting dose of Rivadem Capsules is 1.5 mg twice a day (BID). If this dose is well tolerated, after a minimum of two weeks of treatment, the dose may be increased to 3 mg BID. Subsequent increases to 4.5 mg BID and 6 mg BID should be attempted after a minimum of 2 weeks at the previous dose. If adverse effects (e.g., nausea, vomiting, abdominal pain, loss of appetite) cause intolerance during treatment, the patient should be instructed to discontinue treatment for several doses and then restart at the same or next lower dose level. If treatment is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose . The maximum dose is 6 mg BID (12 mg/day). Rivadem Capsules should be taken with meals in divided doses in the morning and evening.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:
The most commonly reported adverse drug reactions are gastrointestinal, including nausea (38 %)and vomiting (23 %), especially during titration. Female patients are more susceptible than male patients to gastrointestinal adverse drug reactions and weight loss. The following adverse drug reactions, listed below in Table 1, have been accumulated innovator package insert.
Table 1*

	ADVERSE DRUG REACTION				
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**
Psychiatric disorders	-	Agitation Confusion	Insomnia Depression		Hallucinations
Nervous system disorders	Dizziness	Headache Somnolence Tremor	Syncope	Seizures	Extrapyramidal symptoms (including worsening of Parkinson's disease)
Cardiac disorders	-			Angina pectoris	Cardiac arrhythmia
Gastrointestinal disorders	Nausea Vomiting Diarrhoea Loss of appetite	Abdominal pain and dyspepsia		Gastric and duodenal ulcers	Gastrointestinal haemorrhage Pancreatitis
Vascular disorders					Hypertension
Hepato-biliary disorders					Elevated liver function tests
Skin and subcutaneous disorders		Sweating increased		Rashes	
Infections and infestation					Urinary infection
General disorders		Fatigue and asthenia Malaise	Accidental fall		
Investigations		Weight loss			

* Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: Very common >1/10); common >1/100, <1/10); uncommon >1/1,000, <1/100); rare >1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports.

OVERDOSAGE AND THEIR MANAGEMENT:
Symptoms: Most cases of accidental overdosage have not been associated with any clinical signs or symptoms and almost all of the patients concerned continued rivastigmine treatment. Where symptoms have occurred, they have included nausea, vomiting and diarrhoea, hypertension or hallucinations. Due to the known vagotonic effect of cholinesterase inhibitors on heart rate, bradycardia and/or syncope may also occur. Ingestion of 46 mg occurred in one case; following conservative management the patient fully recovered within 24 hours.
Management: As rivastigmine has a plasma half-life of about 1 hour and a duration of acetylcholinesterase inhibition of about 9 hours, it is recommended that in cases of asymptomatic overdose no further dose of rivastigmine should be administered for the next 24 hours. In overdose accompanied by severe nausea and vomiting, the use of antiemetics should be considered. Symptomatic treatment for other adverse events should be given as necessary. In massive overdose, atropine can be used. An initial dose of 0.03 mg/kg intravenous atropine sulphate is recommended, with subsequent doses based on clinical response. Use of scopolamine as an antidote is not recommended.

IDENTIFICATION:
RIVADEM 1.5 MG CAPSULE: Size '2', hard gelatin capsule with opaque yellow cap and opaque yellow body, containing off white to slightly yellow powder.
RIVADEM 3 MG CAPSULE: Size '2', hard gelatin capsule with opaque orange cap and opaque orange body, containing off white to slightly yellow powder.
RIVADEM 4.5 MG CAPSULE: Size '2', hard gelatin capsule with opaque red cap and opaque red body, containing off white to slightly yellow powder.
RIVADEM 6 MG CAPSULE: Size '2', hard gelatin capsule with opaque red cap and opaque orange body, containing off white to slightly yellow powder.

STORAGE INSTRUCTION:
Store below 30°C.

PRESENTATION:
RIVADEM Capsules are packed in Alu-Alu blister of 10 and 7 Capsules. Such blisters containing 10 Capsules are packed into a carton of 10's, 30's , 60's and 100's. Such blisters containing 7 Capsules are packed into a carton of 28's.

Manufactured by:
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.

PRODUCT NAME	:	Rivadem Capsules	**COUNTRY :** Malaysia	**LOCATION :** Indrad		**Supersedes A/W No.:**		
ITEM / PACK	:	Insert	**NO. OF COLORS:** 1	**REMARK :**				
DESIGN STYLE	:	Front/Back	**PANTONE SHADE NOS.:**	**SUBSTRATE :**				
CODE	:	xxxxxxxx-xxxx	Black	**Activities**	**Department**	**Name**	**Signature**	**Date**
DIMENSIONS (MM)	:	180 x 240		Prepared By	**Pkg.Dev**			
ART WORK SIZE	:	S/S		Reviewed By	**Pkg.Dev**			
DATE	:	04-03-2024		Approved By	**Quality**			