

Data Sheet

Name of the Medicine

RIMANE™

Rivastigmine 1.5, 3.0, 4.5 and 6.0 mg capsules

Qualitative and quantitative composition

RIMANE hard capsules contain 1.5, 3.0, 4.5 or 6.0 mg rivastigmine (as the hydrogen tartrate salt).

For a full list of excipients see List of excipients.

Pharmaceutical form

Capsule

Indications

Therapeutic indications

Treatment of patients with mild to moderately severe dementia of the Alzheimer type, also termed probable Alzheimer's Disease or Alzheimer's Disease.

Dosage and method of Administration

Administration

RIMANE should be administered twice a day, with morning and evening meals.

Initial dose

1.5 mg, twice a day

Dose titration

The starting dose is 1.5 mg twice a day. If this dose is well tolerated after a minimum of two weeks of treatment, the dose may be increased to 3 mg twice a day. Subsequent increases to 4.5 mg and then 6 mg twice a day should also be based on good tolerability of the current dose and may be considered after a minimum of two weeks' treatment at that dose level.

If adverse effects (e.g. nausea, vomiting, abdominal pain or loss of appetite) or weight decrease are observed during treatment, these may respond to

omitting one or more doses. If adverse effects persist, the daily dose should be reduced to the previous well-tolerated dose.

Maintenance dose

1.5 to 6 mg twice a day. To achieve maximum therapeutic benefit patients should be maintained on their highest well-tolerated dose.

Recommended maximum daily dose

6 mg twice a day

Re-initiation of therapy

The incidence and severity of adverse events are generally increased with higher doses.

If treatment is interrupted for longer than several days, treatment should be re-initiated with the lowest daily dose and titrated as described above.

Use in children

The use of rivastigmine in children has not been studied and is therefore not recommended.

Use in patients with renal or hepatic impairment

No dose adjustment is necessary in patients with renal or hepatic impairment (see Contraindications).

Contraindications

The use of rivastigmine is contraindicated in patients with known hypersensitivity to rivastigmine, other carbamate derivatives or other ingredients of the formulation (see List of excipients).

Rivastigmine is contra-indicated in patients with severe liver impairment since it has not been studied in this population.

Special warnings and precautions for use

As with other cholinomimetics, care must be taken when using rivastigmine in patients with sick sinus syndrome or conduction defects (sino-atrial block, atrio-ventricular block) (see Adverse effects).

Cholinergic stimulation may cause increased gastric acid secretion and may exacerbate urinary obstruction and seizures. Caution is recommended in treating patients predisposed to such conditions.

Like other cholinomimetics, rivastigmine should be used with caution in

patients with a history of asthma or obstructive pulmonary disease.

Treatment should always be started at a dose of 1.5 mg twice daily and titrated to the patient's maintenance dose. If treatment is interrupted for longer than several days, treatment should be re-initiated with the lowest daily dose to reduce the possibility of adverse reactions (e.g. severe vomiting) (see Dosage and method of administration).

Dose titration: As with other cholinomimetics, adverse effects have been observed shortly after dose increase. They may respond to a dose reduction. In other cases, rivastigmine has been discontinued (see Adverse effects).

Interactions

Rivastigmine is metabolised mainly through hydrolysis by esterases. Minimal metabolism occurs via the major cytochrome P450 isoenzymes. Thus, no pharmacokinetic interactions are anticipated with other drugs metabolised by these enzymes.

No pharmacokinetic interaction was observed between oral 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.

Concomitant administration of rivastigmine with commonly prescribed medications, such as antacids, antiemetics, antidiabetics, centrally acting antihypertensives, β -blockers, calcium channel blockers, inotropic drugs, antianginals, non-steroidal anti-inflammatory drugs, oestrogens, analgesics, benzodiazepines and antihistamines, was not associated with an alteration in the kinetics of rivastigmine, or an increased risk of clinically relevant untoward effects.

In view of its pharmacodynamic effects, rivastigmine should not be given concomitantly with other cholinomimetic drugs and might interfere with the activity of anticholinergic medications.

As a cholinesterase inhibitor, rivastigmine may exaggerate the effects of succinylcholine-type muscle relaxants during anaesthesia.

Precautions

Pregnancy

In animal studies, rivastigmine was not teratogenic. However, the safety of rivastigmine in human pregnancy has not been established, and it should only be given to pregnant women if the potential benefit outweighs the potential risk for the foetus.

Lactation

It is not known if rivastigmine is excreted into human milk, and patients on rivastigmine should therefore not breast-feed.

Effects on ability to drive and use machines

No impairment of motor function has been noted in patients with Alzheimer's disease treated with rivastigmine. However, in patients with dementia treated with rivastigmine, the ability to continue driving or operating complex machines should be routinely evaluated by the treating physician.

Adverse effects

The most commonly reported adverse drug reactions are gastrointestinal including nausea (38%) and vomiting (23%), especially during titration. Female patients in clinical studies were found to be more susceptible to gastrointestinal adverse drug reactions and weight loss.

The following adverse drug reactions, listed below in Table 1, have been accumulated in patients with Alzheimer's dementia treated with rivastigmine.

Table 1

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

Infections and infestations

Very rare: Urinary infection

Psychiatric disorders

Common: Agitation, confusion

Uncommon: Insomnia, depression

Very rare: Hallucinations

Nervous system disorders

Very common: Dizziness

Common: Headache, somnolence, tremor

Uncommon: Syncope

Rare: Seizures

Cardiac disorders

Rare: Angina pectoris, myocardial infarction

Very rare: Cardiac arrhythmia (e.g. bradycardia, atrio-ventricular block, atrial fibrillation and tachycardia)

Vascular disorders

Very rare: Hypertension

Gastrointestinal disorders

Very common: Nausea, vomiting, diarrhoea, loss of appetite

Common: Abdominal pain and dyspepsia

Rare: Gastric and duodenal ulcers

Very rare: Gastrointestinal haemorrhage, mild pancreatitis, severe vomiting associated with oesophageal rupture

Hepatobiliary disorders

Uncommon: Abnormal hepatic function tests

Skin and subcutaneous tissue disorders

Common: Sweating increased

Rare: Rashes

General disorders and administration site conditions

Common: Fatigue and asthenia, malaise

Uncommon: Accidental fall

Investigations

Common: Weight loss

Incompatibilities

Not applicable.

Overdosage

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, diarrhoea, hypertension and 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.

Treatment

As rivastigmine has a plasma half-life of about 1 hour and 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 i.v. atropine sulfate is recommended, with subsequent doses based on clinical response. Use of scopolamine as an antidote is not recommended.

Pharmacology

Pharmacodynamic properties

Pharmacotherapeutic group: brain-selective cholinesterase inhibitor; ATC-code: N06DA03.

Pathological changes in dementia such as Alzheimer's Disease involve cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. These pathways are known to be involved in attention, learning and memory and other cognitive processes. Rivastigmine, a brain-selective acetyl- and butyryl-cholinesterase inhibitor of the carbamate type, is thought to facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by functionally intact cholinergic neurons. Data from animal studies indicate that rivastigmine selectively increases the availability of acetylcholine in the cortex and hippocampus. Thus, rivastigmine may have an ameliorative effect on cholinergic-mediated cognitive deficits associated with Alzheimer's Disease. In addition, there is some evidence that cholinesterase inhibition could slow the formation of amyloidogenic beta-amyloid-precursor protein (APP) fragments, and thus of amyloid plaques, which are one of the main pathological features of Alzheimer's Disease.

Rivastigmine interacts with its target enzymes by forming a covalently bound complex that temporarily inactivates the enzymes. In healthy young men, an oral 3.0 mg dose decreases acetylcholinesterase (AChE) activity in cerebrospinal fluid (CSF) by approximately 40% within the first 1.5 hours after administration. Activity of the enzyme returns to baseline levels about 9 hours after the maximum inhibitory effect has been achieved. Butyrylcholinesterase (BuChE) activity in CSF was transiently inhibited and was no longer different from baseline after 3.6 hours in healthy young volunteers. In patients with Alzheimer's Disease (AD), inhibition of acetylcholinesterase in CSF by rivastigmine was dose-dependent up to 6 mg given twice daily, the highest dose tested. Inhibition of BuChE activity in CSF of AD patients by rivastigmine was similar to that of AChE, with a change from baseline of more than 60% after 6 mg given twice daily. The effect of rivastigmine on AChE and BuChE activity in CSF was sustained after 12 months administration, the longest time studied. Statistically significant correlations were found between the degree of inhibition by rivastigmine of AChE and BuChE in the CSF and changes on a compound measure of cognitive performance in AD patients; however, only BuChE inhibition in CSF was significantly and consistently correlated with improvements in speed-, attention- and memory-related subtests.

Clinical studies in Alzheimer's Dementia

The efficacy of rivastigmine in the treatment of Alzheimer's Disease has been demonstrated in placebo-controlled studies. The patients involved had an MMSE (Mini-Mental State Examination) of 10-24. Results from two pivotal 26-week multicentre studies comparing 1-4 mg/day and 6-12 mg/day with placebo, as well as pooled analysis of Phase III studies have established that rivastigmine produces significant improvement in the major domains of cognition, global functioning and activities of daily living, and in disease severity. Both the low and high dose ranges showed benefit for cognition, global functioning, and disease severity; in addition, the higher dose range produced benefit in activities of daily living.

The following key outcome measures were used in these studies:

Alzheimer's Disease Assessment Scale (ADAS-Cog): a performance-based test system that measures cognitive areas relevant for patients with Alzheimer's Disease such as attention, learning, memory and language;

Clinician Interview Based Impression of Change-Plus (CIBIC-Plus): a clinician-rated assessment of the patient's global change in the domains of cognition, behaviour and functioning, incorporating separate patient and caregiver inputs;

Progressive Deterioration Scale (PDS): a caregiver-rated evaluation of the patient's ability to perform activities of daily living such as toileting, washing, eating, and helping with household chores and shopping.

Study results have indicated that onset of efficacy is generally as early as week 12 and is maintained at the end of 6 months of treatment. Patients treated with 6-12 mg experienced improvement in cognition, activities of daily living and global functioning, while placebo patients showed deterioration. The effects of rivastigmine on these measures (e.g. ADAS-Cog difference from placebo 5 points at week 26) indicate a delay in the rate of deterioration of at least 6 months.

Analyses performed to detect those subtests and symptoms of the ADAS-Cog and CIBIC-Plus, respectively, which improved in patients treated with rivastigmine indicated that all ADAS-Cog subtests (ideational praxis, orientation, test instructions, word recall, language ability and word recognition) and all CIBIC-Plus items, except anxiety, were significantly improved at week 26 with rivastigmine 6-12 mg. Items which improved in at least 15% more rivastigmine than placebo patients completing treatment included word recall, functioning, agitation, tearfulness or crying, delusions, hallucinations, purposeless and inappropriate activities, and physical threats and/or violence.

Pharmacokinetic properties

Absorption

Rivastigmine is rapidly and completely absorbed. Peak plasma concentrations are reached in approximately 1 hour. As a consequence of the drug's interaction with its target enzyme, the increase in bioavailability is about 1.5-fold greater than that expected from the increase in dose. Absolute bioavailability after a 3 mg dose is about 36%. Administration of rivastigmine capsules with food delays absorption (t_{max}) by 90 min and lowers C_{max} and increases AUC by approximately 30%.

Distribution

Rivastigmine is weakly bound to plasma proteins (approximately 40%). It readily crosses the blood brain barrier and has an apparent volume of distribution in the range of 1.8-2.7 l/kg.

Metabolism

Rivastigmine is rapidly and extensively metabolised (half-life in plasma approximately 1 hour), primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite. In vitro, this metabolite shows minimal inhibition of acetylcholinesterase (<10%). Based on evidence from in vitro and animal studies, the major cytochrome P450 isoenzymes are minimally involved in rivastigmine metabolism. Consistent with these observations is the finding that no drug interactions relating to cytochrome P450 have been observed in humans (see Interaction with other medical products and other forms of interaction).

Elimination

Unchanged rivastigmine is not found in the urine; renal excretion of the metabolites is the major route of elimination. Following administration of ^{14}C -rivastigmine, renal elimination was rapid and essentially complete (>90 %) within 24 hours. Less than 1% of the administered dose is excreted in the faeces. There is no accumulation of rivastigmine or the decarbamylated metabolite in patients with Alzheimer's Disease.

Elderly subjects

While bioavailability of rivastigmine is greater in elderly than in young healthy volunteers, studies in Alzheimer patients aged between 50 and 92 years showed no change in bioavailability with age.

Preclinical safety data

Acute toxicity

The estimated oral LD_{50} values in mice were 5.6 mg base/kg (males) and 13.8 mg base/kg (females). The estimated oral LD_{50} values in rats were 8.1 mg

base/kg (males) and 13.8 mg base/kg (females).

Repeated dose toxicity

Studies in rats, mice, dogs and monkeys (maximum doses 3.8, 6.3, 2.5 and 6.3 mg-base/kg/day, respectively) revealed evidence of cholinergic stimulation of the central and peripheral nervous systems. In-life tolerability to rivastigmine was variable between species, with the dog as the most sensitive species. No target organ toxicities or clinical pathology alterations were observed in any species, although gastro-intestinal effects were prominent in dogs.

Mutagenicity

Rivastigmine was not mutagenic in tests for gene mutation, primary DNA damage and chromosomal damage *in vivo*. In tests for chromosomal damage *in vitro*, a small increase in the number of cells carrying chromosomal aberrations occurred at very high concentrations. However, as there was no evidence of clastogenic activity in the more relevant *in vivo* chromosomal damage test, it is most likely that the *in vitro* findings were false positive observations.

Carcinogenicity

No evidence of carcinogenicity was found in studies conducted at dose levels up to 1.1 mg base/kg/day in rats and 1.6 mg base/kg/day in mice.

Reproductive toxicity

Oral studies in pregnant rats and rabbits with dose levels up to 2.3 mg base/kg/day gave no indication of teratogenic potential on the part of rivastigmine. Similarly, there was no evidence of adverse effects of rivastigmine on fertility, reproductive performance or in utero or postnatal growth and development in rats at given dose levels up to 1.1 mg base/kg/day.

Pharmaceutical particulars

List of excipients

1.5 mg capsules

Gelatin, titanium dioxide (E 171), iron oxide, yellow (E 172), magnesium stearate, microcrystalline cellulose, colloidal anhydrous silica, sodium lauryl sulphate, hypromellose

3.0 4.5 and 6.0 mg capsules

Gelatin, titanium dioxide (E 171), iron oxide, yellow (E 172), iron oxide red (E172), magnesium stearate, microcrystalline cellulose, colloidal anhydrous

silica; sodium lauryl sulphate, hypromellose

Storage and Stability

Store below 30°C.

Shelf life

36 months

RIMANE capsules must be kept out of the reach and sight of children.

Presentation

Carton of blisters containing 30 tablets. HDPE bottles containing 100 tablets.

Medicine classification

Prescription Medicine

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