ALRIVA
Rivastigmine Capsules
P1513406

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SUMMARY OF PRODUCT CHARACTERISTICS

ALRIVA

Rivastigmine Capsules 1.5 mg, 3 mg.

RX only

NAME OF THE DRUG PRODUCT: Rivastigmine Capsules 1.5 mg
Rivastigmine Capsules 3 mg

(TRADE) NAME OF THE DRUG PRODUCT: ALRIVA 1.5 mg
ALRIVA 3 mg

STRENGTH: 1.5 mg, 3 mg,

PHARMACEUTICAL DOSAGE FORM: Capsule.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Rivastigmine Capsules 1.5 mg:

Each capsule contains Rivastigmine tartrate equivalent to Rivastigmine 1.5 mg.

Rivastigmine Capsules 3 mg:

Each capsule contains Rivastigmine tartrate equivalent to Rivastigmine 3 mg.

PHARMACEUTICAL FORM

Rivastigmine Capsules 1.5 mg: Yellow cap and yellow body colored size '2' capsules imprinted in black ink with 'H' on cap and '67 on body, containing white to off-white granular powder.

Rivastigmine Capsules 3 mg: Orange cap and orange body colored size '2' capsules imprinted in black ink with 'H' on cap and '68 on body, containing white to off-white granular powder.

CLINICAL PARTICULARS

Therapeutic indications:

Treatment of patients with mild to moderately severe dementia of alzeimer's type, also termed probable Alzheimer's disease. Treatment of patients with mild to moderately severe dementia associated with Parkinson's disease.

Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's dementia or dementia associated with Parkinson's disease. Diagnosis should be made according to current guidelines. Therapy with rivastigmine should only be started if a caregiver is available who will regularly monitor intake of the medicinal product by the patient.

Rivastigmine should be administered twice a day, with morning and evening meals. The capsules should be swallowed whole.

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 of treatment at that dose level.

If adverse reactions (e.g. nausea, vomiting, abdominal pain or loss of appetite), weight decrease or worsening of extrapyramidal symptoms (e.g. tremor) in patients with dementia associated with Parkinson's disease are observed during treatment, these may respond to omitting one or more doses. If adverse reactions persist, the daily dose should be temporarily reduced to the previous well-tolerated dose or the treatment may be discontinued.

Maintenance dose

The effective dose is 3 to 6 mg twice a day; to achieve maximum therapeutic benefit patients should be maintained on their highest well tolerated dose. The recommended maximum daily dose is 6 mg twice a day.

Maintenance treatment can be continued for as long as a therapeutic benefit for the patient exists. Therefore, the clinical benefit of rivastigmine should be reassessed on a regular basis, especially for patients treated at doses less than 3 mg twice a day. If after 3 months of maintenance dose treatment the patient's rate of decline in dementia symptoms is not altered favourably, the treatment should be discontinued. Discontinuation should also be considered when evidence of a therapeutic effect is no longer present.

Re-initiation of therapy

If treatment is interrupted for more than several days, it should be re-initiated at 1.5 mg twice daily. Dose titration should then be carried out as described above.

Renal and hepatic impairment

No dose adjustment is necessary for patients with mild to moderate renal or hepatic impairment. However, due to increased exposure in these populations dosing recommendations to titrate according to individual tolerability should be closely followed as patients with clinically significant renal or hepatic impairment might experience more adverse reactions (see section Special warnings and precautions for use and Pharmacokinetic properties).

Patients with severe hepatic impairment have not been studied (see section Special warnings and precautions for use).

Children

Rivastigmine is not recommended for use in children.

Contraindications

The use of this medicinal product is contraindicated in patients with hypersensitivity to the active substance, other carbamate derivatives or to any of the excipients used in the formulation.

Special warnings and precautions for use

The incidence and severity of adverse reactions 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 reactions (e.g. hypertension and hallucinations in patients with Alzheimer's dementia and worsening of extrapyramidal symptoms, in particular tremor, in patients with dementia associated with Parkinson's disease) have been observed shortly after dose increase. They may respond to a dose reduction. In other cases, Rivastigmine has been discontinued (see section Undesirable effects).

Gastrointestinal disorders such as nausea, vomiting and diarrhoea are dose-related, and may occur particularly when initiating treatment and/or increasing the dose (see section Undesirable effects). These adverse reactions occur more commonly in women. Patients who show signs or symptoms of dehydration resulting from prolonged vomiting or diarrhoea can be managed with intravenous fluids and dose reduction or discontinuation if recognised and treated promptly. Dehydration can be associated with serious outcomes.

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.

In case of severe vomiting associated with rivastigmine treatment, appropriate dose adjustments as recommended in section Posology and method of administration must be made. Some cases of severe vomiting were associated with oesophageal rupture (see section Undesirable effects). Such events appeared to occur particularly after dose increments or high doses of rivastigmine.

Care must be taken when using rivastigmine in patients with sick sinus syndrome or conduction defects (sino-atrial block, atrio-ventricular block) (see section Undesirable effects).

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 a 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 use of rivastigmine in patients with severe dementia of Alzheimer's disease or associated with Parkinson's disease, other types of dementia or other types of memory impairment (e.g. age-related cognitive decline) has not been investigated and therefore use in these patient populations is not recommended.

Like other cholinomimetics, rivastigmine may exacerbate or induce extrapyramidal symptoms. Worsening (including bradykinesia, dyskinesia, gait abnormality) and an increased incidence or severity of tremor have been observed in patients with dementia associated with Parkinson's disease (see section Undesirable effects). These events led to the discontinuation of rivastigmine in some cases (e.g. discontinuations due to tremor 1.7% on rivastigmine vs 0% on placebo). Clinical monitoring is recommended for these adverse reactions.

Driving and using machines Alzheimer's and Parkinson's disease dementia may cause gradual impairment of driving performance or compromise the ability to use machinery. Rivastigmine may induce dizziness and somnolence, mainly when initiating treatment or increasing the dose. Therefore, in patients with dementia treated with Rivastigmine, the ability to continue driving or operating complex machines should be routinely evaluated by the treating physician.

Special populations

Patients with clinically significant renal or hepatic impairment might experience more adverse reactions (see section Posology and method of administration and Pharmacokinetic properties). Patients with severe hepatic impairment have not been studied. However, Rivastigmine may be used in this patient population and close monitoring is necessary. Patients with body weight below 50 kg may experience more adverse reactions and may be more likely to discontinue due to adverse reactions

QT 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 OT prolongation, or concomitant use with medicinal products known to induce QT prolongation and/or torsade de pointes. Clinical monitoring may also be required.

Interaction with other medicinal products and other forms of interaction

As a cholinesterase inhibitor, rivastigmine may exaggerate the effects of succinylcholine-type muscle relaxants during anaesthesia. Caution is recommended when selecting anaesthetic agents. Possible dose adjustments or temporarily stopping treatment can be considered if needed.

In view of its Pharmacodynamic effects, rivastigmine should not be given concomitantly with other cholinomimetic substances and might interfere with the activity of anticholinergic medicinal products.

No pharmacokinetic 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 interactions with other medicinal products appear unlikely, although rivastigmine may inhibit the butyrylcholinesterase mediated metabolism of other substances.

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, and erythromycin). Clinical monitoring may also be required.

Pregnancy and lactation

For rivastigmine no clinical data on exposed pregnancies are available. No effects on fertility or embryofoetal development were observed in rats 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.

In animals, rivastigmine is excreted into milk. It is not known if rivastigmine is excreted into human milk. Therefore, women on rivastigmine should not breast-feed.

Effects on ability to drive and use machines

Alzheimer's disease may cause gradual impairment of driving performance or compromise the ability to use machinery. Furthermore, rivastigmine can induce dizziness and somnolence, mainly when initiating treatment or increasing the dose.

As a consequence, rivastigmine has minor or moderate influence on the ability to drive and use machines. Therefore, the ability of patients with dementia on rivastigmine to continue driving or operating complex machines should be routinely evaluated by the treating physician.

Undesirable effects

The most commonly reported adverse reactions are gastrointestinal, including nausea and vomiting, especially during titration. Female patients were found to be more susceptible than male patients to gastrointestinal adverse reactions and weight loss. The following table represents the adverse reactions have been accumulated in patients with Alzheimer's dementia treated with Rivastigmine.

Infections and infestations Very rare	 Urinary infection
Metabolism and nutrition disorders Very common Not known	 Anorexia Dehydration
Psychiatric disorders Common Common Common Uncommon Uncommon Very rare Not known	 Agitation Confusion Anxiety Insomnia Depression Hallucinations Aggression, restlessness
Nervous system disorders Very common Common Common Common Uncommon Rare Very rare	 Dizziness Headache Somnolence Tremor Syncope Seizures Extrapyramidal symptoms (including worsening of Parkinson's disease)

A/s: 210 x 420 mm ■ Black

AUROBINDO Packaging Development	Product Name ALRIVA	Component Leaflet	Item Code P1513406	Date & Time 15.05.2024 & 03.30 pm
	Customer / Country Malaysia_Unit 7	Version No. 17	Reason Of Issue NEW	Reviewed / Approved by
Team Leader: Kiran Kumar Initiator: Shirisha N	Dimensions 210 x 420 mm	No. of Colours : 01		
Artist: SCD	Pharmacode 13406	13406		
Additional Information :				Sign / Date

Cardiac disorders Rare Very rare Not known	 Angina pectoris Cardiac arrhythmia (e.g. bradycardia, atrio- ventricular block, atrial fibrillation and tachycardia) Sick sinus syndrome
Vascular disorders Very rare	 Hypertension
Gastrointestinal disorders Very common Very common Very common Common Rare Very rare Very rare Not known	 Nausea Vomiting Diarrhoea Abdominal pain and dyspepsia Gastric and duodenal ulcers Gastrointestinal haemorrhage Pancreatitis Some cases of severe vomiting were associated with oesophageal rupture (see section Special warnings and precautions for use).
Hepatobiliary disorders Uncommon Not known	 Elevated liver function tests Hepatitis
Skin and subcutaneous tissue disorders Common Rare Not known	 Hyperhydrosis Rash Pruritus
General disorders and administration site conditions Common Common Uncommon	 Fatigue and asthenia Malaise Fall
Investigations common	 Weight loss

The following table shows the adverse reactions reported in patients with dementia associated with Parkinson's disease treated with Rivastigmine.

Metabolism and nutrition disorders Common Common	 Anorexia Dehydration
Psychiatric disorders Common Common Common Not known	 Insomnia Anxiety Restlessness Aggression
Nervous system disorders Very common Common Common Common Common Common Common Uncommon	 Tremor Dizziness Somnolence Headache Worsening of Parkinson's disease Bradykinesia Dyskinesia Dystonia
Cardiac disorders Common Uncommon Uncommon Not known	 Bradycardia Atrial Fibrillation Atrioventricular block Sick sinus syndrome
Gastrointestinal disorders Very common Very common Common Common Common	 Nausea Vomiting Diarrhoea Abdominal pain and dyspepsia Salivary hypersecretion
Hepatobiliary disorders Not known	 Hepatitis
Skin and subcutaneous tissue disorders Common	 Hyperhydrosis
Musculoskeletal and connective tissue disorders Common	 Muscle rigidity
General disorders and administration site conditions Common Common	 Fatigue and asthenia Gait abnormality

Overdose

Symptoms

Most cases of accidental overdose 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.

Treatment

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 reactions 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Rivastigmine is an acetyl- and butyrylcholinesterase inhibitor of the carbamate type, thought to facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by functionally intact cholinergic neurones. Thus, rivastigmine may have an ameliorative effect on cholinergic-mediated cognitive deficits in dementia associated with Alzheimer's disease and Parkinson'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 mg dose decreases acetylcholinesterase (AChE) activity in 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. In patients with Alzheimer's disease, inhibition of AChE in CSF by rivastigmine was dose-dependent up to 6 mg given twice daily, the highest dose tested. Inhibition of butyrylcholinesterase activity in CSF of 14 Alzheimer patients treated by rivastigmine was similar to that of AChE.

Pharmacokinetic properties

Absorption

Rivastigmine is rapidly and completely absorbed. Peak plasma concentrations are reached in approximately 1 hour. As a consequence of rivastigmine'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%±13%. Administration of rivastigmine with food delays absorption (tmax) by 90 min and lowers Cmax and increases AUC by approximately 30%.

Distribution

Protein binding of rivastigmine is 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. Total plasma clearance of rivastigmine was approximately 130 l/h after a 0.2 mg intravenous dose and decreased to 70 l/h after a 2.7 mg intravenous dose.

Excretion

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.

Subjects with hepatic impairment

The Cmax of rivastigmine was approximately 60% higher and the AUC of rivastigmine was more than twice as high in subjects with mild to moderate hepatic impairment than in healthy subjects.

Subjects with renal impairment

Cmax and AUC of rivastigmine were more than twice as high in subjects with moderate renal impairment compared with healthy subjects; however there were no changes in Cmax and AUC of rivastigmine in subjects with severe renal impairment.

PHARMACEUTICAL PARTICULARS

List of excipients

Microcrystalline cellulose, Hypromellose, Silica, colloidal anhydrous & Magnesium stearate

Composition of the head and body of the capsules:

Gelatin, Yellow iron oxide (E172), Red iron oxide (E172), Titanium dioxide (E 171), Purified Water & Sodium lauryl sulfate.

Black ink print:

Shellac & Black Iron oxide (E172)

Incompatibilities

Not applicable.

Shelf life

Please refer outer package for expiry date.

Special precautions for storage

Store below 30°C.

Dosage form and Packaging available

Capsules & Blister of 7 Capsules.

Manufactured by:

AUROBINDO

Aurobindo Pharma Ltd.

Unit-VII, SEZ, TSIIC, Plot. No. SI,
Survey No's : 411/P, 425/P, 434/P, 435/P & 458/P,
Green Industrial Park, Polepally village, Jedcherla Mandal,
Mahaboob Nagar District, Telangana State, India.

Product registration Holder
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