PI for KYRIZ CAPSULES

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

KYRIZ CAPSULES 1.5 mg

KYRIZ CAPSULES 3 mg

KYRIZ CAPSULES 4.5 mg

KYRIZ CAPSULES 6 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

KYRIZ CAPSULES 1.5 mg

Each capsule contains rivastigmine tartrate equivalent to 1,5 mg rivastigmine base. Sugar free.

KYRIZ CAPSULES 3 mg

Each capsule contains rivastigmine tartrate equivalent to 3 mg, rivastigmine base. Sugar free.

KYRIZ CAPSULES 4.5 mg

Each capsule contains rivastigmine tartrate equivalent to 4.5 mg, rivastigmine base. Sugar free.

KYRIZ CAPSULES 6 mg

Each capsule contains rivastigmine tartrate equivalent to 6 mg, rivastigmine base. Sugar free.

Excipients:

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Oral capsule.

KYRIZ CAPSULES 1.5 mg:

Yellow/Yellow size ‘2’ hard gelatine capsules containing white to off-white powder with “CL7” on cap and “1.5” on body imprinted in red ink.

KYRIZ CAPSULES 3 mg:

Orange/Orange size ‘2’ hard gelatine capsules containing white to off-white powder with “CL8” on cap and “3” on body imprinted in red ink.

KYRIZ CAPSULES 4.5 mg:

Red/Red size ‘2’ hard gelatine capsules containing white to off-white powder with “CL9” on cap and “4.5” on body imprinted in white ink.

KYRIZ CAPSULES 6 mg:

Red/Orange size ‘2’ hard gelatine capsules containing white to off-white powder with “CL10” on cap and “6” on body imprinted in white ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of mild to moderately severe Alzheimer's dementia. Symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease.

4.2 Posology and method of administration

Treatment should be initiated and supervised by a medical practitioner 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.

Posology:

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.

Individual response to rivastigmine cannot be predicted. However, a greater treatment effect was seen in Parkinson's disease patients with moderate dementia. Similarly a larger effect was observed in Parkinson's disease patients with visual hallucinations (see section 5.1).

Treatment effect has not been studied in placebo-controlled trials beyond 6 months.

Re-initiation of therapy

If treatment is interrupted for more than three 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 dose-dependent adverse reactions. Patients with severe hepatic impairment have not been studied, however, rivastigmine capsules may be used in this patient population provided close monitoring is exercised (see sections 4.4 and 5.2).

Paediatric population

There is no relevant use of rivastigmine in the paediatric population in the treatment of Alzheimer's disease.

Method of administration

For oral use.

4.3 Contraindications

The use of this medicinal product is contraindicated in patients with known hypersensitivity to the active substance rivastigmine, to other carbamate derivatives or to any of the excipients listed in section 6.1. Previous history of application site reactions suggestive of allergic contact dermatitis with rivastigmine patch (see section 4.4).

4.4 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 three days, it should be re-initiated at 1.5 mg twice daily to reduce the possibility of adverse reactions (e.g. vomiting).

Patients who develop application site reactions suggestive of allergic contact dermatitis to rivastigmine patch and who still require rivastigmine treatment should only be switched to oral rivastigmine after negative allergy testing and under close medical supervision. It is possible that some patients sensitised to rivastigmine by exposure to rivastigmine patch may not be able to take rivastigmine in any form.

There have been rare reports of patients experiencing allergic dermatitis (disseminated) when administered rivastigmine irrespective of the route of administration (oral, transdermal). In these cases, treatment should be discontinued (see section 4.3).

Patients and caregivers should be instructed accordingly.

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 4.8).

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 4.8). 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 4.2 must be made. Some cases of severe vomiting were associated with oesophageal rupture (see section 4.8). 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 4.8).

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, a predisposition to hypokalaemia or hypomagnesaemia,

or concomitant use with medicinal products known to induce QT prolongation and/or torsade de pointes (see sections 4.5 and 4.8).

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.

Rivastigmine 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.

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 4.8). 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.

Special populations

Patients with clinically significant renal or hepatic impairment might experience more adverse reactions (see sections 4.2 and 5.2). Dosing recommendations to titrate according to individual tolerability must be closely followed. 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.

4.5 Interaction with other medicines and other forms of interaction

Rivstigmine 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 and possible additive effects, rivastigmine should not be given concomitantly with other cholinomimetic substances. Rivastigmine might interfere with the activity of anticholinergic medicinal products (e.g. oxybutynin, tolterodine).

Additive effects leading to bradycardia (which may result in syncope) have been reported with the combined use of various beta-blockers (including atenolol) and rivastigmine. Therefore, caution should be exercised when rivastigmine is combined with beta-blockers and also other bradycardia agents (e.g.class III antiarrhythmic agents, calcium channel antagonists, digitalis glycoside, pilocarpin).

Since bradycardia constitutes a risk factor in the occurrence of torsades de pointes, the combination of rivastigmine with torsades de pointes-inducing medicinal products such as antipsychotics i.e. some phenothiazines (chlorpromazine, levomepromazine), benzamides (sulpiride, sultopride, amisulpride, tiapride, veralipride), pimozide, haloperidol, droperidol, cisapride, citalopram, diphemanil, erythromycin IV, halofantrin, mizolastin, methadone, pentamidine and moxifloxacine should be observed with caution and clinical monitoring (ECG) may also be required.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

In pregnant animals, rivastigmine and/or metabolites crossed the placenta. It is not known if this occurs in humans. No clinical data on exposed pregnancies are available. Inperi/postnatal studies in rats, an increased gestation time was observed. Rivastigmine should not be used during pregnancy.

Breast-feeding

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

Fertility

No adverse effects of rivastigmine were observed on fertility or reproductive performance in rats. Effects of rivastigmine on human fertility are not known.

4.7 Effects on ability to drive and use machines

Rivastigmine can induce dizziness and somnolence, mainly when initiating treatment or increasing the dose. Patients experiencing dizziness or somnolence should avoid driving and operation of machines.

4.8 Undesirable effects

Summary of the reported safety profile

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

Adverse reactions in Table 1 and Table 2 are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: frequent (≥1/10 to <1/100); less frequent (≥1/100 to <1/10,000); frequency not known (cannot be estimated from the available data).

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

Table 1: Tabulated summary of adverse events.

System organ class	**Frequency**	**Undesirable effect**
Infections and infestations	Less frequent	Urinary infection
Metabolic and nutrition disorders	Frequent	Anorexia Decreased appetite
	Frequency unknown	Dehydration
Psychiatric disorders	Frequent	Agitation Confusion Anxiety Nightmares
	Less frequent	Insomnia Depression Hallucinations
	Frequency unknown	Aggression, restlessness
Nervous system disorders	Frequent	Dizziness Headache Somnolence Tremor
	Less frequent	Syncope Seizures Extrapyramidal symptoms (including worsening of Parkinson's disease)

Cardiac disorder	Less frequent	Angina pectoris Cardiac arrhythmia (e.g. bradycardia, atrioventricular block, atrial fibrillation and tachycardia)
	Frequency unknown	Sick sinus syndrome
Vascular disorders	Less frequent	Hypertension
Gastrointestinal disorders	Frequent	Nausea Vomiting Diarrhoea Abdominal pain and dyspepsia
	Less frequent	Gastric and duodenal ulcers Gastrointestinal haemorrhage Pancreatitis
	Frequency unknown	Some cases of severe vomiting were associated with oesophageal rupture (see section 4.4).
Hepatobiliary disorders	Less frequent	Elevated liver function tests
	Frequency unknown	Hepatitis
Skin and subcutaneous tissue disorders	Frequent	Hyperhydrosis
	Less frequent	Rash
	Frequency unknown	Pruritis, allergic dermatitis (disseminated)
General disorders and administration site conditions	Frequent	Fatigue and asthenia Malaise
	Less frequent	Fall

Investigations	Frequent	Weight loss

Table 2 shows the adverse reactions reported during clinical studies conducted in patients with dementia associated with Parkinson's disease treated with rivastigmine capsules.

Table 2: Tabulated summary of adverse events.

System organ class	**Frequency**	**Undesirable effect**
Metabolism and nutrition disorders	Frequent	Decreased appetite Dehydration
Psychiatric disorders	Frequent	Insomnia Anxiety Restlessness Hallucination, visual Depression
	Frequency unknown	Aggression
Nervous system disorders	Frequent	Tremor Dizziness Somnolence Headache Parkinson's disease (worsening) Bradykinesia Dyskinesia Hypokinesia Cogwheel rigidity
	Less frequent	Dystonia

Cardiac disorder	Frequent	Bradycardia
	Less frequent	Arial fibrillation Atrioventricular block
	Frequency unknown	Sick sinus syndrome
Vascular disorders	Frequent	Hypertension
	Less frequent	Hypotension
Gastrointestinal disorders	Frequent	Nausea Vomiting Diarrhoea Abdominal pain and dyspepsia Salivary hypersecretion
Hepatobiliary disorders	Frequency unknown	Hepatitis
Skin and subcutaneous tissue disorders	Frequent	Hyperhydrosis
	Frequency unknown	Allergic dermatitis
General disorders and administration site conditions	Frequent	Fall Fatigue and asthenia Gait disturbance Parkinson gait

The following are pre-defined adverse events that may reflect worsening of parkinsonian symptoms in patients with dementia associated with Parkinson's disease

Frequent:

- Tremor
- Fall
- Parkinson's disease (worsening)

Less frequent:

- Salivary hypersecretion
- Dyskinesia
- Parkinsonism
- Hypokinesia
- Movement disorder
- Bradykinesia
- Dystonia
- Gait abnormality
- Muscle rigidity
- Balance disorder
- Musculoskeletal stiffness
- Rigors
- Motor dysfunction

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions & Quality Problem Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/index/8.

4.9 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 24 hours after the overdose.

Cholinergic toxicity has been reported with muscarinic symptoms that are observed with moderate poisonings such as miosis, flushing, digestive disorders including abdominal pain, nausea, vomiting and diarrhoea, bradycardia, bronchospasm and increased bronchial secretions, hyperhidrosis, involuntary urination and/or defecation, lacrimation, hypotension and salivary hypersecretion.

In more severe cases nicotinic effects might develop such as muscular weakness, fasciculations, seizures and respiratory arrest with possible fatal outcome.

Additionally there have been post-marketing cases of dizziness, tremor, headache, somnolence, confusional state, hypertension, hallucinations and malaise.

Management

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 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.

5. PHARMACOLOGICAL PROPERTIES

A 5.3 Cholinomimetics (cholinergics)

ATC code: N06DA03

5.1 Pharmacodynamic 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.

5.2 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 over the dose range 1 to 3 mg. Absolute bioavailability after a 3 mg dose is about 36 %. Administration of rivastigmine with food delays absorption (t_{max}) by 90 minutes 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 medicine interactions related to cytochrome P450 have been observed in humans (see Section 4.5)

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.

Subjects with hepatic impairment

The C_{max} 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

C_{max} 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 C_{max} and AUC of rivastigmine in subjects with severe renal impairment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, hypromellose, colloidal silicon dioxide, magnesium stearate, gelatine, titanium dioxide (C.I. no. 77891) and purified water.

In addition, **KYRIZ CAPSULES 1.5 mg** contain iron oxide yellow (C.I. no. 77492) and **KYRIZ CAPSULES 3 mg, 4.5 mg and 6 mg** contain iron oxide yellow (C.I. no. 77492) and iron oxide red (C.I. No. 77491).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months from the date of manufacturing for HDPE 60s pack

36 months from the date of manufacturing for other packs

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blisters in the carton until required for use.

Keep HDPE containers tightly closed.

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

KYRIZ CAPSULES 1.5 mg, 3.0 mg, 4.5 mg and 6.0 mg:

1) Blister pack:

Cold form laminate (composed of 25 micron OPA/45 micron aluminium foil/60 micron PVC) and plain 30 micron aluminium foil with 6-8 GSM heat seal lacquer

Pack size: 10's – Each carton contains 10 blisters of 10 capsules each.

2) HDPE Container Pack:

60 ml, round white HDPE bottle with 33-400 neck finish closed with a white 33 mm child resistant with pulp and heat seal closure.

Pack size: 60's - One HDPE container contains 60 capsules.

Not all pack sizes will be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd

Office Block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8. REGISTRATION NUMBER(S)

KYRIZ 1,5 MG : 47/5.3/0210

KYRIZ 3 MG : 47/5.3/0211

KYRIZ 4,5 MG : 47/5.3/0212

KYRIZ 6 MG : 47/5.3/0213

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 August 2020

10. DATE OF REVISION OF THE TEXT

02 MAY 2023

PM0056-01

Vanita Rajool

Digitally signed by Vanita Rajool
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