APPROVED PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S5

PROPRIETARY NAME AND DOSAGE FORM

ARIMENTIA 5 mg (film-coated tablet)

ARIMENTIA 10 mg (film-coated tablet)

COMPOSITION

Each film-coated tablet of ARIMENTIA 5 mg contains 5 mg of donepezil hydrochloride.

Excipients:

Hydroxypropylcellulose, lactose monohydrate, magnesium stearate, maize starch, microcrystalline cellulose, polyethylene glycol, titanium dioxide (C.I. 77891)

Contains sugar: Lactose monohydrate 91,75 mg

Each film-coated tablet of ARIMENTIA 10 mg contains 10 mg of donepezil hydrochloride.

Excipients:

Hydroxypropylcellulose, lactose monohydrate, magnesium stearate, maize starch, microcrystalline cellulose, polyethylene glycol, titanium dioxide (C.I. 77891)

Contains sugar: Lactose monohydrate 183,5 mg

CATEGORY AND CLASS

A 5.3 Cholinomimetics (cholinergics)

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Donepezil hydrochloride is a reversible inhibitor of acetylcholinesterase, the predominant cholinesterase in the brain. Donepezil hydrochloride is over 1 000 times more potent an inhibitor of this enzyme than of butyrylcholinesterase, an enzyme which is present mainly outside the central nervous system.

In patients with Alzheimer's dementia participating in clinical trials, administration of single daily doses of 5 mg or 10 mg of donepezil hydrochloride produced steady-state inhibition of acetylcholinesterase activity (measured in erythrocyte membranes) of 63,6 % and 77,3 % respectively when measured post dose. The inhibition of acetylcholinesterase (AChE) in red blood cells by donepezil hydrochloride has been shown to correspond closely to the effects in the cerebral cortex. In addition, significant correlation was demonstrated between plasma levels of donepezil hydrochloride, AChE inhibition and change in ADAS-cog, a sensitive and well validated scale which examines cognitive performance - including memory, orientation, attention, reason, language and praxis.

Pharmacokinetic properties

Absorption

Oral administration of donepezil hydrochloride produces predictable plasma concentrations with maximal values achieved approximately 3 to 4 hours after dose administration. Plasma concentrations and area under the curve rise in proportion to the dose. The terminal disposition half-life is approximately 70 hours; thus administration of multiple single-daily doses results in gradual approach to steady state. Approximate

steady state is achieved within 3 weeks after the initiation of therapy. Once at steady state, plasma donepezil hydrochloride concentrations and the related pharmacodynamic activity show little variability over the course of the day.

Neither food nor time of administration (morning versus evening dose) affect the absorption of donepezil hydrochloride.

Distribution

The steady state volume of distribution is 12 l/kg. Donepezil hydrochloride is approximately 96 % bound to human plasma proteins. The distribution of donepezil hydrochloride in various body tissues has not been definitively studied. However, in a mass balance study conducted in healthy male volunteers, 240 hours after the administration of a single 5 mg dose of ^{14}C-labelled donepezil hydrochloride, approximately 28 % of the label remained unrecovered.
This suggests that donepezil hydrochloride and/or any of its metabolites may persist in the body for more than 10 days. The average CSF:plasma ratio for both doses, expressed as a percent of the concentration in plasma, was 15,7 %.

Metabolism/Excretion

Donepezil hydrochloride is both excreted in the urine intact and metabolised by the cytochrome P450 system to multiple metabolites, not all of which have been identified.

Following administration of a single 5 mg dose of ^{14}C-labelled donepezil hydrochloride, plasma radioactivity, expressed as a percent of the administered dose, was present primarily as intact donepezil hydrochloride (30 %), 6-O desmethyl donepezil (11 % - the only metabolite that exhibits activity similar to donepezil hydrochloride), donepezil-cis-N-oxide (9 %), 5-O-desmethyl donepezil (7 %) and the glucuronide conjugate of 5-O

desmethyl donepezil (3 %). Approximately 57 % of the total administered radioactivity was recovered from the urine and 14,5 % was recovered from the faeces, suggesting biotransformation and urinary excretion as the primary routes of elimination.

There is no evidence to suggest enterohepatic recirculation of donepezil hydrochloride and/or any of its metabolites. Plasma donepezil concentrations decline with a half-life of approximately 70 hours. Sex, race and smoking history have no clinically significant influence on plasma concentrations of donepezil hydrochloride.

Mechanism of Action

Current theories on the pathogenesis of the cognitive signs and symptoms of Alzheimer's disease attribute some of them to a deficiency of cholinergic neurotransmission. Donepezil hydrochloride 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 acetylcholinesterase. If this proposed mechanism of action is correct, donepezil's effect may lessen as the disease process advances and fewer cholinergic neurons remain intact. There is no evidence that donepezil alters the course of the underlying process. The enzyme AChE also occurs peripherally in red blood cells; therefore, measurement of AChE activity in erythrocyte membranes provides an index for donepezil hydrochloride pharmacodynamics. This surrogate marker has been evaluated in several human pharmacokinetic/pharmacodynamic trials and in controlled clinical trials. The population plasma donepezil hydrochloride concentrations and AChE inhibition measurements verified that patients in clinical trials experienced exposure to donepezil hydrochloride and its pharmacodynamic actions as predicted.

Results from therapeutic medicine monitoring showed no apparent relationship between plasma concentration and adverse medicine reactions.

INDICATIONS

ARIMENTIA tablets are indicated for the symptomatic treatment of mild or moderate dementia in Alzheimer's disease.

CONTRAINDICATIONS

ARIMENTIA is contraindicated in:

- Patients with a known hypersensitivity to donepezil hydrochloride, piperidine derivatives, or to any excipients in ARIMENTIA (see COMPOSITION).
- Pregnancy and lactation as the safety of ARIMENTIA has not been established.
- Children. ARIMENTIA is not recommended for use in children.

WARNINGS AND SPECIAL PRECAUTIONS

Alzheimer's dementia

Treatment should be initiated by a doctor experienced in the treatment of Alzheimer's dementia.

Maintenance treatment can be continued for as long as a therapeutic benefit for the patient exists.

Therefore, the clinical benefit of ARIMENTIA should be reassessed on a regular basis.

Discontinuation should be considered when evidence of a therapeutic effect is no longer present. Individual response to ARIMENTIA cannot be predicted.

The use of ARIMENTIA in patients with severe dementia, other types of dementia or other types of memory impairment (e.g. age related cognitive decline) has not been established.

Anaesthesia

ARIMENTIA, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia.

Cardiovascular conditions

Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate (e.g. bradycardia). The potential for this action may be particularly important to patients with “sick sinus syndrome” or other supraventricular cardiac conduction conditions such as sinoatrial or atrioventricular block. Syncopal episodes and seizures have been reported in association with the use of ARIMENTIA.

In such patients the possibility of heart block or long sinusal pauses should be considered.

Gastrointestinal conditions

Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk of developing ulcers e.g. those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs). Data of donepezil hydrochloride, as contained in ARIMENTIA, have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

ARIMENTIA, as a predictable consequence of its pharmacological properties, produces diarrhoea, nausea and vomiting. These effects, when they occur, appear more frequently with the 10 mg/day dose than with the 5 mg/day dose. In most cases, these effects may be mild and transient, sometimes lasting one to three weeks, and resolve during continued use of ARIMENTIA.

Genitourinary

ARIMENTIA, a cholinomimetic may cause bladder outflow obstruction.

Neurological conditions

Seizures - Cholinomimetics are believed to have some potential to cause generalised convulsions. However, seizure activity may also be a manifestation of Alzheimer's disease.

Cholinomimetics may have the potential to exacerbate or induce extrapyramidal symptoms.

Neuroleptic Malignant Syndrome (NMS)

NMS, a potentially life-threatening condition characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels, has been reported to occur in association with donepezil, particularly in patients also receiving concomitant antipsychotics. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. If a patient develops signs and symptoms indicative of NMS or presents with unexplained high fever without additional clinical manifestations of NMS, treatment should be discontinued.

Pulmonary conditions

Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. The administration of ARIMENTIA concomitantly with other inhibitors of acetylcholinesterase, agonists or antagonists of the cholinergic system should be avoided.

Severe hepatic impairment

There are no data for patients with severe hepatic impairment.

Effects on ability to drive and use machines

Since adverse reactions such as dizziness, somnolence and blurred vision have been reported in patients receiving ARIMENTIA, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that ARIMENTIA does not adversely affect their ability to do so (see SIDE EFFECTS).

Excipients

Lactose warning:

ARIMENTIA contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take ARIMENTIA.

INTERACTIONS

Use with anticholinergics: Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

Use with cholinomimetics and other cholinesterase inhibitors: A synergistic effect may be expected when cholinesterase inhibitors, such as ARIMENTIA are given concurrently with succinylcholine, similar neuromuscular blocking medicines or cholinergic agonists such as bethanechol.

Beta-blocking medicines have an effect on cardiac conduction but an *in vivo* study showed

that donepezil, as in ARIMENTIA, has minimal effects on hydrolysis of succinylcholine.

Medicines highly bound to plasma proteins: Displacement studies have been performed *in-vitro* between this highly bound medicine (96 %) and other medicines such as furosemide, digoxin and warfarin. Donepezil hydrochloride at concentrations of 0,3 to 10 µg/ml did not affect the binding of furosemide (5 µg/ml), digoxin (2 µg/ml), and warfarin (3 µg/ml) to human albumin. Similarly, the binding of donepezil hydrochloride, as contained in ARIMENTIA, to human albumin was not affected by furosemide, digoxin and warfarin.

Effect of donepezil hydrochloride, as contained in ARIMENTIA on the metabolism of other medicines: No *in vivo* clinical trials have investigated the effect of donepezil hydrochloride on the clearance of medicines metabolised by CYP 3A4 (e.g. cisapride, terfenadine) or by CYP 2D6 (e.g. imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean Ki about 50 to 130 µM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference.

Whether donepezil hydrochloride, as contained in ARIMENTIA, has any potential for enzyme induction is not known.

Donepezil hydrochloride, as contained in ARIMENTIA, and its metabolites do not inhibit the metabolism of theophylline, cimetidine, warfarin, digoxin, thioridazine, risperidone and sertraline.

In a study of Parkinson's disease patients on optimal treatment with L-dopa/carbidopa, administration of donepezil hydrochloride, as contained in ARIMENTIA, for 21 days had no effects on L-dopa/carbidopa, blood levels. No effects on motor activity were also observed

in this study.

Effect of other medicines on the metabolism of ARIMENTIA: Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil, as contained in ARIMENTIA metabolism *in vitro*. Therefore these and other CYP3A4 inhibitors, such as itraconazole and erythromycin, and CYP2D6 inhibitors such as fluoxetine could inhibit the metabolism of ARIMENTIA. Whether there is a clinical effect of these inhibitors is not known. In a study in healthy volunteers, ketoconazole increased mean donepezil concentrations by 30 %. These increases are smaller than those produced by ketoconazole for other medicine sharing the CYP3A4 pathway and are not likely to be clinically relevant.

Administration of donepezil, as contained in ARIMENTIA, had no effect on the pharmacokinetics of ketoconazole. Inducers of CYP2D6 and CYP3A4 (e.g. phenytoin, carbamazepine, alcohol, dexamethasone, rifampicin and phenobarbitone) could increase the rate of elimination of ARIMENTIA.

HUMAN REPRODUCTION

The safety of ARIMENTIA in pregnancy and lactation has not been established (see CONTRAINDICATIONS).

Pregnancy

There are no adequate data from the use of donepezil as contained in ARIMENTIA in pregnant women.

The potential risk for humans is unknown.

ARIMENTIA should not be used during pregnancy unless clearly necessary.

Lactation

It is not known whether donepezil as contained in ARIMENTIA is excreted in human breast milk and there are no studies in lactating women. Therefore, women on ARIMENTIA should not breastfeed.

DOSAGE AND DIRECTIONS FOR USE

Treatment is initiated at 5 mg/day (once-a-day dosing). ARIMENTIA should be taken orally, in the evening, just prior to retiring.

The 5 mg/day dose should be maintained for at least one month in order to allow the earliest clinical responses to treatment to be assessed and to allow steady-state concentrations of ARIMENTIA to be achieved. Following a one-month clinical assessment of treatment at 5 mg/day, the dose of ARIMENTIA can be increased to 10 mg/day (once-a-day dosing). The maximum recommended daily dose is 10 mg. Doses greater than 10 mg/day have not been studied in clinical trials.

Upon discontinuation of treatment, a gradual abatement of the beneficial effects of ARIMENTIA is seen. There is no evidence of a rebound effect after abrupt discontinuation of therapy.

Renal and Hepatic Impairment:

A similar dose schedule can be followed for patients with renal impairment as clearance of ARIMENTIA is not affected by these conditions.

Due to increased exposure in mild to moderate hepatic impairment dose titration should

be performed according to individual tolerability. There are no data for patients with severe hepatic impairment.

SIDE EFFECTS

Metabolism and nutrition disorders

Frequent: Anorexia

Less frequent: Dehydration

Psychiatric disorders

Frequent: Insomnia, nightmares, agitation, delusions, depression, hallucinations, abnormal dreams

Less frequent: Irritability, aggression, increased libido, restlessness, nervousness

Frequency unknown: Confusion

Nervous system disorders

Frequent: Dizziness, somnolence, headache

Less frequent: Syncope, tremor, paraesthesia, ataxia, aphasia, extrapyramidal symptoms, seizures, neuroleptic malignant syndrome

Ear and labyrinth disorders

Less frequent: Vertigo

Eye disorders

Less frequent: Cataract, eye irritation, blurred vision

Cardiac disorders

Less frequent: Angina, sino-atrial and atrioventricular (AV) blocks, atrial fibrillation, bradycardia

Vascular disorders

Less frequent: Hypertension, vasodilation, hot flushes, hypotension

Respiratory, thoracic and mediastinal disorders

Less frequent: Dyspnoea, sore throat

Gastrointestinal disorders

Frequent: Nausea, diarrhoea, vomiting, abdominal disturbance, dyspepsia, faecal incontinence, toothache

Less frequent: Gastrointestinal bleeding, bloating, epigastric pain, peptic ulcers, gastric ulcers, salivary hypersecretion

Hepatobiliary disorders

Less frequent: Hepatitis, liver dysfunction

Skin and subcutaneous tissue disorders

Frequent: Rash, pruritus

Less frequent: Diaphoresis, urticaria, ecchymosis

Musculoskeletal, connective tissue and bone disorders

Frequent: Muscle cramps

Less frequent: Rhabdomyolysis

Injury, poisoning and procedural complications

Less frequent: Bone fracture, accident

Renal and urinary disorders

Frequent: Frequent urination

Less frequent: Urinary incontinence, nocturia

Frequency unknown: Bladder outflow obstruction

Infections and infestations

Frequent: Urinary tract infection, influenza, common cold

Less frequent: Bronchitis

Investigations

Frequent: Weight loss

Frequency unknown: Minor increases in serum creatinine kinase

General disorders and administrative site conditions

Frequent: Fatigue, pain (various locations)

Less frequent: Arthritis, chest pain, abnormal crying

The most common adverse events are largely predicted by ARIMENTIA's cholinomimetic effects.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

Symptoms

Dose-related signs of cholinergic stimulation were observed in animals and included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, fasciculation and lower body surface temperature.

Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterised by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory

depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.

Treatment

As in any case of overdose, general supportive measures should be utilised. Tertiary anticholinergics such as atropine may be used as an antidote for ARIMENTIA overdosage.

Intravenous atropine sulphate titrated to effect is recommended: an initial dose of 1,0 mg to 2,0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether donepezil hydrochloride, as contained in ARIMENTIA, and/or its metabolites can be removed by dialysis, haemodialysis, peritoneal dialysis, or haemofiltration.

IDENTIFICATION

ARIMENTIA 5 mg:

White, film-coated round tablet, with score line on one side and plain on the other side, with a diameter of 7,0 mm to 7,4 mm.

ARIMENTIA 10 mg:

White, film-coated round tablet, with score line on one side and plain on the other side, with a diameter of 9,0 mm to 9,4 mm.

PRESENTATION

7, 10, 14, 28, 30, 56, 60, 84, 98, 100 tablets are packed in a silver polyvinyl chloride/polyvinylidene chloride blister strip sealed with an aluminium foil backing. The blister strips are packed into an outer cardboard carton. 100 or 250 tablets are packed in a

white polypropylene container with a polyethylene snap on closure with a tear off tamper evident strip.

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store at or below 25 °C protected from light and moisture.

Keep container tightly closed.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

ARIMENTIA 5 mg: 43/5.3/0487

ARIMENTIA 10 mg: 43/5.3/0488

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead, 2191

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

Date of registration:

ARIMENTIA 5 mg: 30 September 2011

ARIMENTIA 10 mg: 30 September 2011

Date of the most recent amendment to the professional information as approved by the Authority: 30 September 2011

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