SCHEDULING STATUS: S5

PROPRIETARY NAME AND DOSAGE FORM:

ARICEPT® 5 mg (Tablets)

ARICEPT® 10 mg (Tablets)

COMPOSITION:

Each ARICEPT 5 mg tablet contains 5 mg donepezil hydrochloride.

Each ARICEPT 10 mg tablet contains 10 mg donepezil hydrochloride.

ARICEPT tablets contain the following inactive ingredients: lactose monohydrate, maize starch, microcrystalline cellulose, hydroxypropyl cellulose and magnesium stearate. The film coating contains talc, polyethylene glycol, hydroxypropyl methycellulose and titanium dioxide. Additionally, the 10 mg tablet contains yellow iron oxide (synthetic) as a colouring agent.

PHARMACOLOGICAL CLASSIFICATION:

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.

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 drug monitoring showed no apparent relationship between plasma concentration and adverse drug reactions.

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 is hepatically metabolised and the predominant route for the elimination of both the parent drug and its metabolites is renal, as 79 % of the recovered dose was found in the urine with the remaining 21 % in the faeces. Moreover, the parent compound, donepezil, is the predominant elimination product in urine. The major metabolites of donepezil include M1 and M2 (via *O*-dealkylation and hydroxylation), M11 and M12 (via glucuronidation of M1 and M2 respectively), M4 (via hydrolysis) and M6 (via *N*-oxidation).

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.

INDICATIONS:

ARICEPT tablets are indicated for the symptomatic treatment of dementia of Alzheimer's disease.

CONTRAINDICATIONS:

ARICEPT is contraindicated in patients with a known hypersensitivity to donepezil hydrochloride, piperidine derivatives, or to any excipients used in the formulation.

Safety and efficacy of ARICEPT has not been established in children; therefore it is not recommended for use in children.

WARNINGS AND SPECIAL PRECAUTIONS:

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 ARICEPT should be reassessed on a regular basis. Discontinuation should be considered when evidence of a therapeutic effect is no longer present. Individual response to ARICEPT cannot be predicted.

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

Anaesthesia:

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

Cardiovascular conditions:

Due to 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 have been reported in association with the use of ARICEPT.

Gastrointestinal conditions:

Cholinomimetics may promote gastric acid production. 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 non-steroidal anti-inflammatory drugs (NSAIDs). Clinical studies of ARICEPT have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

ARICEPT, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhoea, nausea and vomiting. These effects, when they occur, appeared more frequently with the 10 mg/day dose than with the 5 mg/day dose. In most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of ARICEPT.

Genitourinary:

Although not observed in clinical trials of ARICEPT, cholinomimetics may cause bladder outflow obstruction.

Neurological conditions:

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

Pulmonary conditions:

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

Effects on ability to drive and use machines:

Dementia may cause impairment of driving performance or compromise the ability to use machinery. Furthermore, ARICEPT can induce fatigue, dizziness and muscle cramps, mainly when initiating or increasing the dose. The treating doctor should routinely evaluate the ability of patients on ARICEPT to continue driving or operating complex machines.

INTERACTIONS:

Medicines highly bound to plasma proteins:

Drug displacement studies have been performed *in vitro* between this highly bound medicine (96 %) and other medicines such as furosemide, digoxin and warfarin. ARICEPT at concentrations of 0,3 – 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 ARICEPT to human albumin was not affected by furosemide, digoxin and warfarin.

Effect of ARICEPT on the metabolism of other medicines:

No *in vivo* clinical trials have investigated the effect of ARICEPT on the clearance of medicines metabolised by CYP3A4 (e.g. cisapride, terfenadine) or by CYP2D6 (e.g. imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean Ki about 50 – 130 µM), that, given the therapeutic plasma concentrations of ARICEPT (164 nM), indicates little likelihood of interference.

Whether ARICEPT has any potential for enzyme induction is not known. ARICEPT and/or any of its metabolites do not inhibit the metabolism of theophylline, warfarin, cimetidine, digoxin, thioridizine, risperidone and sertraline in humans. In a study of Parkinson's disease patients on optimal treatment with L-dopa/carbidopa, administration of ARICEPT for 21 days had no effects on L-dopa or carbidopa blood levels. In this study, no effects on motor activity were observed.

Based on *in vitro* studies, ARICEPT shows little or no evidence of direct inhibition of CYP2B6, CYP2C8 and CYP2C19 at clinically relevant concentrations.

Effect of other medicines on the metabolism of ARICEPT:

Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit ARICEPT 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 ARICEPT. Whether there is a clinical effect of these inhibitors is not known. In a study in healthy volunteers, ketoconazole increased mean ARICEPT concentrations by 30 %. These increases are smaller than those produced by ketoconazole for other agents sharing the CYP3A4 pathway and are not likely to be clinically relevant. Administration of ARICEPT had no effect on the pharmacokinetics of ketoconazole. Inducers of CYP2D6 and CYP3A4 (e.g. phenytoin, carbamazepine, alcohol, dexamethasone, rifampicin and phenobarbital) could increase the rate of elimination of ARICEPT.

Formal pharmacokinetic studies demonstrated that the metabolism of ARICEPT is not significantly affected by concurrent administration of digoxin, cimetidine, thioridazine, risperidone or sertraline.

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 are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol or beta blocking agents which have an effect on cardiac conduction, but an *in vitro* study showed that ARICEPT had minimal effects on hydrolysis of succinylcholine.

ARICEPT was not a substrate of P-glycoprotein in an *in vitro* study.

PREGNANCY AND LACTATION:

The safety of ARICEPT in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

Adults/ elderly:

The dosages of ARICEPT shown to be effective in controlled clinical trials are 5 mg and 10 mg administered once daily. Although there is no statistically significant evidence that a greater treatment effect is obtained from the use of the 10 mg dose, there is a suggestion, based on analysis of group data that some additional benefits may accrue to some patients from the use of the higher dose. ARICEPT should be taken orally, in the evening, just prior to retiring. Treatment is initiated at 5 mg/day (once-a-day dosing).

The 5 mg/day dose should be maintained for at least 4 – 6 weeks in order to allow the earliest clinical responses to treatment to be assessed and to allow steady-state concentrations of ARICEPT to be achieved. Following a one-month clinical assessment of treatment at 5 mg/day, the dose of ARICEPT 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 ARICEPT 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 or mild to moderate hepatic impairment as clearance of ARICEPT is not affected by these conditions.

SIDE EFFECTS:

The adverse events defined as occurring in patients receiving 10 mg/day and twice the placebo rate, are largely predicted by ARICEPT's cholinomimetic effects. The table below reflects the incidence of adverse events in patients receiving treatment with ARICEPT for all stages of Alzheimer's disease.

The table below contains adverse events categorized as follows utilizing the incidence rates: Very common ≥ 1/10 (≥ 10 %); Common ≥ 1/100 and < 1/10 (≥ 1 % and < 10 %); Uncommon ≥ 1/1 000 and <

1/100 (≥ 0,1 % and < 1 %), Rare ≥ 1/10 000 and < 1/1 000 (≥ 0,01 % and < 0,1 %); Very rare < 1/10 000 (< 0,01 %).

MedDRA System Organ Class	**Frequency**	**Undesirable effects**
Infections and infestations	Common	Common cold, influenza
Metabolism and nutrition disorders	Uncommon	Dehydration
Psychiatric disorders	Common	Abnormal dreams, agitation, delusions, depression, hallucinations, insomnia
	Uncommon	Abnormal crying, aggressive behaviour, increased libido, irritability, nervousness, restlessness
Nervous system disorders	Common	Dizziness, headache, somnolence
	Uncommon	Aphasia, ataxia, paraesthesia, syncope, tremor
	Rare	Seizure
Eye disorders	Uncommon	Cataract, eye irritation, vision blurred
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Uncommon	Atrioventricular block, bradycardia
	Rare	Sinoatrial block
Vascular disorders	Uncommon	Hot flushes, hypertension, hypotension, vasodilation
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea, sore throat
Gastrointestinal disorders	Common	Abdominal disturbance, anorexia, diarrhoea, faecal incontinence, nausea, vomiting
	Uncommon	Bloating, epigastric pain, gastrointestinal haemorrhage, toothache
	Rare	Duodenal ulcer, gastric ulcer
Hepatobiliary disorders	Rare	Hepatitis

Skin and subcutaneous tissue disorders	Uncommon	Diaphoresis, ecchymosis, pruritus, urticaria
Musculoskeletal and connective tissue disorders	Common	Muscle cramps
Renal and urinary disorders	Common	Frequent urination
	Uncommon	Nocturia, urinary incontinence
General disorders and administration site conditions	Common	Fatigue, pain
	Uncommon	Chest pain
Investigations	Common	Weight decrease
	Rare	Minor increases in serum concentrations of muscle creatine kinase
Injury, poisoning and procedural complications	Uncommon	Accident, bone fracture

There is evidence to suggest that the frequency of these common adverse events may be affected by rate of dose titration.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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.

As in any case of overdose, general supportive measures should be utilised. Tertiary anticholinergics such as atropine may be used as an antidote for ARICEPT overdosage. Intravenous atropine sulphate titrated to effect is recommended: an initial dose of 1,0 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 ARICEPT and/or its metabolites can be removed by dialysis (haemodialysis, peritoneal dialysis, or haemofiltration).

IDENTIFICATION:

ARICEPT 5 mg: White, round, biconvex, film-coated tablets embossed with the word “ARICEPT” on the one side and “5” on the other side

ARICEPT 10 mg: Yellow, round, biconvex, film-coated tablets embossed with the word “ARICEPT” on the one side and “10” on the other side

PRESENTATION:

ARICEPT 5 mg tablets: Blister strips (PVC/foil) of 2 x 14

ARICEPT 10 mg tablets: Blister strips (PVC/foil) of 2 x 14

STORAGE INSTRUCTIONS:

Store below 30 °C. Keep out of the reach of children.

REGISTRATION NUMBERS:

ARICEPT 5 mg tablets: 32/5.3/0315

ARICEPT 10 mg tablets: 32/5.3/0316

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

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton, 2196

South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

1. Last Council Approval: 09 May 2013
2. Compliance with regulation 9 & 10: 15 February 2017

NAMIBIA: S3

Aricept 5 mg: Reg. No.: 04/5.3/1232

Aricept 10 mg: Reg. No.: 04/5.3/1233