SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

DONECEPT 5 (5 mg, tablets)

DONECEPT 10 (10 mg, tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DONECEPT 5: Each tablet contains 5 mg donepezil hydrochloride 5 mg.

Contains sugar: lactulose monohydrate 49 mg per tablet

DONECEPT 10: Each tablet contains 10 mg donepezil hydrochloride 10 mg.

Contains sugar: lactulose monohydrate 98 mg per tablet

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Tablets

DONECEPT 5: White coloured, circular, biconvex, film-coated tablet with “5” debossed on one side and “DPZ” debossed on the other side.

DONECEPT 10: Yellow coloured, circular, biconvex, film-coated tablet with “10” debossed on one side and “DPZ” debossed on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DONECEPT is indicated in the following:

- For the symptomatic treatment of mild or moderate dementia in Alzheimer's disease.

4.2 Posology and method of administration

Posology

DONECEPT 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 donepezil hydrochloride to be achieved.

Following a one-month clinical assessment of treatment at 5 mg/day, the dose of DONECEPT 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. Upon discontinuation of treatment, a gradual abatement of the beneficial effects of DONECEPT is seen. There is

no evidence of a rebound effect after abrupt discontinuation of therapy.

Special populations

Renal & hepatic impairment:

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

Due to possible increased exposure in mild to moderate hepatic impairment, dose titration should be performed according to individual tolerability. There is no data for patients with severe hepatic impairment.

Method of administration

DONECEPT should be taken orally, in the evening, just prior to retiring.

4.3 Contraindications

DONECEPT is contraindicated in the following:

- In patients with a known hypersensitivity to donepezil hydrochloride, piperidine derivatives, or to any excipients used in DONECEPT.
- In pregnant and lactating women.
- DONECEPT is not recommended for use in children.

4.4 Special warnings and precautions for use

Treatment should be initiated and supervised by a medical doctor experienced in the diagnosis and treatment of Alzheimer's dementia. Maintenance treatment can be continued for as long as a therapeutic benefit for the patient exists.

The clinical benefit of DONECEPT should be reassessed on a regular basis. Discontinuation should be considered when evidence of a therapeutic effect is no longer present.

Individual response to DONECEPT cannot be predicted. The use of DONECEPT in patients with severe Alzheimer's dementia, other types of dementia or other types of memory impairment (e.g. age-related cognitive decline), has not been established.

Anaesthesia:

DONECEPT, as a cholinesterase inhibitor, may cause exaggeration of succinylcholine-type muscle relaxation during anaesthesia.

Cardiovascular conditions:

Owing to their pharmacological action, cholinesterase inhibitors, such as DONECEPT, 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 DONECEPT. In investigating such patients, the possibility of heart block or long sinusal pauses should be considered.

There have been post-marketing reports of cardiac conduction conditions including atrioventricular block, QTc interval prolongation and Torsades de Pointes (see **section 4.5** and **4.8**). Caution is advised in patients with pre-existing or family history of QTc prolongation, in patients treated with medicines affecting the QTc interval, or in patients with relevant pre-existing cardiac disease (e.g. uncompensated heart failure, recent myocardial infarction, bradyarrhythmias), or electrolyte disturbances (hypokalaemia, hypomagnesaemia). Clinical monitoring (ECG) may be required.

Gastrointestinal conditions:

Cholinesterase inhibitors, such as DONECEPT, 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- non-steroidal anti-inflammatory drugs (NSAIDS).

DONECEPT has been shown to produce diarrhoea, nausea and vomiting. These effects occur 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 DONECEPT.

Genitourinary:

DONECEPT may cause bladder outflow obstruction.

Neurological conditions:

Seizures - DONECEPT may cause generalised convulsions.

Pulmonary conditions:

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

Lactose

DONECEPT contains lactulose. Patients with rare hereditary conditions of galactose intolerance e.g., galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take DONECEPT, which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

The effects of other medicines on the metabolism of DONECEPT:

Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil 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 donepezil.

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 medicines sharing the CYP-3A4 pathway and are not likely to be clinically relevant.

Administration of donepezil, such as DONECEPT, 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 DONECEPT.

The effects of anticholinergics:

Because of their mechanism of action, cholinesterase inhibitors, such as DONECEPT, have the potential to interfere with the activity of anticholinergic medications.

The effects of cholinomimetics and other cholinesterase inhibitors:

A synergistic effect may be expected when cholinesterase inhibitors, such as DONECEPT, are given concurrently with succinylcholine, similar neuromuscular blocking medicines or cholinergic medicines, such as bethanechol.

A synergistic effect may also be expected with beta blocking agents, which have an effect on cardiac conduction.

Other Interaction

Cases of QTc interval prolongation and Torsade de Pointes have been reported as in DONECEPT (see **section 4.4** and **4.8**). Caution is advised when donepezil is used in

combination with other medicines known to prolong the QTc interval and clinical monitoring may be required. Examples include:

- Class IA antiarrhythmics (e.g. disopyramide, quinidine)
- Class III antiarrhythmics (e.g. amiodarone, sotalol)
- Certain antidepressants (e.g. citalopram, escitalopram, amitriptyline)
- Other antipsychotics (e.g. phenothiazine derivatives, pimozide, ziprasidone)
- Certain antibiotics (e.g. clarithromycin, erythromycin, moxifloxacin)

4.6 Fertility, pregnancy and lactation

The use of DONECEPT is not recommended during pregnancy and lactation as safety and efficacy have not been established.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Tabulated summary of adverse reactions

The following adverse reactions have been classified according to the following categories, frequent, less frequent and frequency unknown.

MedDRA system organ Class	**Frequency**	**Side effects**
Infections and infestations	Frequent	Cold, Influenza

Metabolism and nutritional disorders	Less frequent	Dehydration
Psychiatric disorders	Frequent	Abnormal dreams, agitation, delusions, depression, hallucinations, insomnia.
	Less frequent	Abnormal crying, aggression, increased libido, irritability, restlessness, nervousness.
Nervous system disorders	Frequent	Dizziness, headache, somnolence
	Less frequent	Seizure. syncope, tremor, paraesthesia, ataxia, aphasia
Eye disorders	Frequent	Cataract, eye irritation, blurred vision.
Ear and labyrinth disorders	Less frequent	Vertigo
Cardiac disorders	Less frequent	Atrioventricular block, bradycardia, sinoatrial block.
	Frequency not known	Polymorphic ventricular tachycardia including Torsade de Pointes; electrocardiogram QT interval prolonged
Vascular disorders	Less frequent	Hypertension, vasodilation, hot flushes, hypotension.
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea, sore throat, bronchitis.

Gastrointestinal disorders	Frequent	Abdominal disturbance, anorexia, diarrhoea, faecal incontinence, nausea, vomitting.
	Less frequent	Gastrointestinal bleeding, bloating, epigastric pain, duodenal ulcer, gastric ulcer.
Hepatobiliary disorders	Less frequent	Hepatitis.
Skin and subcutaneous tissue disorders	Less frequent	Pruritis, diaphoresis, urticaria, ecchymoses.
Musculoskeletal and connective tissue disorders	Frequent	Muscle cramps.
	Less frequent	Bone fracture.
Renal and urinary disorders	Frequent	Frequent urination.
	Less frequent	Urinary incontinence, nocturia.
General disorders	Frequent	Fatigue, pain.
	Less frequent	Chest pain, toothache.
Investigations	Frequent	Weight decrease.
	Less frequent	Minor increase in serum concentrations of muscle creatinine kinase.

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 Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 and to Cipla Medpro (Pty) Ltd at drugsafetysa@cipla.com or telephone 080 222 6662 (toll free).

4.9 Overdose

The median lethal dose of donepezil hydrochloride, such as in DONECEPT, following administration of a single oral dose in mice and rats is 45 and 32 mg/kg respectively, or approximately 225 and 160 times the maximum recommended human dose of 10 mg per day. 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, such as DONECEPT, 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.

Anticholinergics, such as atropine, may be used as an antidote for DONECEPT overdosage. Intravenous atropine sulphate titrated to effect is recommended: and 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 donepezil hydrochloride and/or its metabolites can be removed by dialysis (haemodialysis, peritoneal dialysis, or haemofiltration).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: A 5.3 Cholinomimetics (cholinergics).

Mechanism of action

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

Theories about 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.

Thus 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.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, donepezil 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. Food or the time of administration does not affect the absorption of donepezil hydrochloride.

Distribution

Steady state volume of distribution of donepezil hydrochloride Is 12 L/kg. Donepezil hydrochloride is approximately 96 % bound to human plasma proteins.

Biotransformation/Elimination

Donepezil hydrochloride is excreted in the urine intact and also 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 % - 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 significant 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Lactulose monohydrate
- Microcrystalline cellulose
- Starch
- Cross carmellose sodium
- Colloidal anhydrous silica
- Magnesium stearate
- Opadry white 04F58804 (containing Hydroxy propyl methyl cellulose, titanium dioxide & macrogol 6000)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C. Store in a well closed container. Protect from light.

Keep the blisters in the outer carton until required for use.

6.5 Nature and contents of container

DONECEPT 5: A transparent PVC/PE/PVDC and aluminium foil blister strip of 10 tablets packed in 30's.

DONECEPT 10: A transparent PVC/PE/PVDC and aluminium foil blister strip of 10 tablets packed in 30's.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Rosen Heights

Pasita Street

Rosen park

Bellville

7530

RSA

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

DONECEPT 5: 42/5.3/0490

DONECEPT 10: 42/5.3/0491

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 April 2010

10. DATE OF REVISION OF THE TEXT

02 March 2023