SCHEDULING STATUS S5

1. NAME OF THE MEDICINE

DONECEPT ODT 5 orally disintegrating tablets

DONECEPT ODT 10 orally disintegrating tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains sugar: lactose monohydrate (spray dried) 131.25 mg per tablet.

Contains sweetener: aspartame 5 mg per tablet

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

Contains sugar: lactose monohydrate (spray dried) 262.5 mg per tablet.

Contains sweetener: aspartame 10 mg per tablet

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

3. PHARMACEUTICAL FORM

Orally disintegrating tablets**.**

DONECEPT ODT 5: White to off-white round, flat tablets with bevelled edges, embossed with ‘5’ on one side and plain on the other.

DONECEPT ODT 10**:** White to off-white round, flat tablets with bevelled edges, embossed with ‘10’ on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DONECEPT ODT orally disintegrating tablets are indicated for the symptomatic treatment of dementia associated with Alzheimer's disease.

4.2 Posology and method of administration

Posology

Adults/Elderly:

The dosages of DONECEPT ODT that are effective 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. Treatment should be initiated at 5 mg/day once daily.

The 5 mg/day dose should be maintained for at least 4 to 6 weeks in order to allow the earliest clinical responses to treatment to be assessed and to allow steady state concentrations of DONECEPT ODT to be achieved.

Following a one-month clinical assessment of treatment at 5 mg/day, the dose may 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 ODT is seen. There is no evidence of a rebound effect after abrupt discontinuation of therapy.

Special populations

Patients with renal and hepatic impairment:

Similar dosing can be followed for patients with renal or mild to moderate hepatic impairment as the clearance of DONECEPT ODT is not affected by these conditions.

Method of administration

DONECEPT ODT is for oral administration.

DONECEPT ODT should be taken in the evening, just prior to retiring. The tablet should be placed on the tongue and allowed to disintegrate before swallowing with or without water, according to patient preference.

4.3 Contraindications

DONECEPT ODT is contraindicated in:

- Patients with known hypersensitivity to donepezil hydrochloride, piperidine derivatives, or any of the excipients of DONECEPT ODT (see **section 6.1**).
- Safety and efficacy of DONECEPT ODT has not been established in children, therefore it is not recommended for use in children and adolescents below 18 years of age.

4.4 Special warnings and precautions for use

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 DONECEPT ODT 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 ODT cannot be predicted.

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

Anaesthesia:

Cholinesterase inhibitors such as DONECEPT ODT is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia.

Cardiovascular conditions:

Owing 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 and seizures have been reported in association with the use of DONECEPT ODT. 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 Torsade 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 drugs 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:

Cholinomimetics such as DONECEPT ODT may promote the production of gastric acid. Patients should therefore be closely monitored for symptoms of active or occult gastrointestinal bleeding, especially those at an 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 ODT, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhoea, nausea and vomiting. These effects are likely to occur more frequently with the 10 mg/day

dose than the 5 mg/day dose. In most cases, these effects are mild and transient, sometimes lasting one to three weeks, and are resolved during continued use of DONECEPT ODT.

Genitourinary:

Cholinomimetics, including DONECEPT ODT, may cause bladder outflow obstruction.

Neurological conditions:

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

Cholinomimetics such as DONECEPT ODT 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 very rarely 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, treatment with DONECEPT ODT should be discontinued.

Pulmonary conditions:

Due to their cholinomimetic actions, cholinesterase inhibitors such as DONECEPT ODT should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. The administration of

DONECEPT ODT 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.

DONECEPT ODT 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, total lactase deficiency or glucose-galactose malabsorption should not take DONECEPT ODT.

DONECEPT ODT contains aspartame. Aspartame is a source of phenylalanine. It may be harmful to patients who have phenylketonuria (PKU).

4.5 Interaction with other medicines and other forms of interaction

Medicines highly bound to plasma proteins

DONECEPT ODT does not affect the binding of furosemide, digoxin and warfarin to human albumin. Similarly, the binding of DONECEPT ODT to human albumin is not affected by furosemide, digoxin and warfarin.

Effect of DONECEPT ODT on the metabolism of other medicines

DONECEPT ODT has a low rate of binding to enzymes such as CYP3A4 and CYP2D6. There is therefore little likelihood of interference with medicines metabolised by these enzymes such as cisapride, terfenadine and imipramine.

The potential for DONECEPT ODT to induce enzymes is not known.

DONECEPT ODT has little or no direct inhibition of CYP2C8, CYP2C19 and CYP2B6 at clinically relevant concentrations.

DONECEPT ODT and/or any of its metabolites do not inhibit the metabolism of theophylline, warfarin, cimetidine, digoxin, thioridazine, risperidone and sertraline in humans.

When taken concurrently for up to 21 days, DONECEPT ODT has no effect on L-dopa or carbidopa blood levels. There are also no effects on motor activity.

Effect of other medicines on the metabolism of DONECEPT ODT

Medicines such as ketoconazole and quinidine (inhibitors of CYP450, CYP3A4 and CYP2D6 respectively), itraconazole and erythromycin (inhibitors of CYP3A4), and fluoxetine (inhibitor of CYP2D6) could all inhibit the metabolism of DONECEPT ODT.

Inducers of CYP2D6 and CYP3A4 such as phenytoin, carbamazepine, alcohol, dexamethasone, rifampicin and phenobarbitone could increase the rate of elimination of DONECEPT ODT.

Use with anticholinergics

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

Use with cholinomimetics and other cholinesterase inhibitors

A synergistic effect may be expected when cholinesterase inhibitors such as DONECEPT ODT are given concurrently with succinylcholine, similar neuromuscular blocking medicines or cholinergic agonists such as bethanechol or beta blocking medicines which have an effect on cardiac conduction. DONECEPT ODT does however have minimal effect on the hydrolysis of succinylcholine.

DONECEPT ODT is not a substrate of P-glycoprotein.

Cases of QTc interval prolongation and Torsade de Pointes have been reported for donepezil. Caution is advised when donepezil is used in combination with other medicinal products known to prolong the QTc interval and clinical monitoring(ECG) 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, sertindole, pimozide, ziprasidone)

Certain antibiotics (e.g. clarithromycin, erythromycin, levofloxacin, moxifloxacin)

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of DONECEPT ODT in pregnancy has not been established.

Studies of donepezil in animals have not shown teratogenic effect but have shown pre and post-natal toxicity. The potential for human risk is unknown.

Lactation

The safety of DONECEPT ODT in lactation has not been established.

Donepezil is excreted in the milk of rats. It is not known whether donepezil hydrochloride is excreted in human breast milk and there are no studies conducted in lactating women. Therefore, women taking DONECEPT ODT should not breastfeed.

Fertility

There are no data on the effect of DONECEPT ODT on fertility.

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 ODT 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 ODT to continue driving or operating complex machines.

4.8 Undesirable effects

Summary of side effect profile

The most common undesirable effects associated with DONECEPT ODT are somnolence, headache and nausea.

Tabulated list of adverse reactions

The following adverse reactions have been classified according to the following categories: “Frequent, less frequent and frequency not known”.

MeDRA System Organ Class	**Frequency**	**Side effects**
Infections and infestations	Frequent	Common cold, influenza
Metabolism and nutrition disorders	Frequent	Anorexia
	Less frequent	Dehydration

Psychiatric disorders	Frequent	Abnormal dreams and nightmares, agitation, delusions, depression, hallucinations, insomnia
	Less frequent	Abnormal crying, aggressive behaviour, increased libido, irritability, nervousness, restlessness
Nervous system disorders	Frequent	Headache, dizziness, somnolence, insomnia
	Less frequent	Aphasia, ataxia, paraesthesia, syncope, tremor, seizure
Eye disorders	Less 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	Hot flushes, hypertension, vasodilation, hypotension
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea, sore throat
Gastrointestinal disorders	Frequent	Abdominal disturbance, anorexia, diarrhoea, faecal incontinence, nausea, vomiting
	Less frequent	Bloating, epigastric pain, gastrointestinal haemorrhage, toothache, gastric duodenal ulcers, salivary hypersecretion
Hepato-biliary disorders	Less frequent	Hepatitis
Skin and subcutaneous tissue disorders	Frequent	Rash
	Less frequent	Diaphoresis, ecchymosis, pruritus, urticaria
Musculoskeletal and connective tissue disorders	Frequent	Muscle cramps
	Less Frequent	Rhabdomyolysis

Renal and urinary disorder	Frequent	Frequent urination
	Less frequent	Nocturia, urinary incontinence
General disorders and administration site conditions	Frequent	Fatigue, pain
	Less frequent	Chest pain
Investigations	Frequent	Weight decrease
	Less frequent	Minor increases in serum concentrations of muscle creatine kinase
Injury and poisoning	Less Frequent	Accident, bone fracture

The frequency of these adverse effects may be affected by the dose titration of DONECEPT ODT.

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found under SAHPRA's publications: http://www.sahpra.org.za/Publications/Index/8 and to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com

4.9 Overdose

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.

General supportive measures should be utilised. Tertiary anticholinergics such as atropine may be used as an antidote for DONECEPT ODT overdosage. Intravenous atropine sulphate titrated to effect is recommended at an initial dose of 1,0 to 2,0 mg IV with subsequent doses based on 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 DONECEPT ODT and/or its metabolites can be removed by dialysis (haemodialysis, peritoneal dialysis, or haemofiltration).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: 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 over 1000 times more potent an inhibitor of this enzyme than butyrylcholinesterase, an enzyme present mainly outside the central nervous system.

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.

The inhibition of acetylcholinesterase (AChE) in red blood cells by donepezil hydrochloride corresponds closely to the effects in the cerebral cortex. In addition, there is significant correlation between plasma levels of donepezil hydrochloride, AChE inhibition and changes in ADAS-cog, a sensitive and well validated scale which examines cognitive performance- including memory, orientation, reason, language and praxis.

Current theories on the pathogenesis 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. 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.

There is no apparent relationship between plasma concentration and adverse drug reactions.

5.2 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 plasma protein binding of the active metabolite 6-O-desmethyl donepezil is not

known. The distribution of donepezil hydrochloride in various body tissues has not been definitively studied. However, donepezil hydrochloride and/or its metabolites may persist in the body for more than 10 days.

Biotransformation

Donepezil is hepatically metabolised by the cytochrome P450 system to multiple metabolites. The major metabolites of donepezil include 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**.**

Elimination

The predominant route for the elimination of both the parent compound and its metabolites is renal, as 79 % of the recovered dose is found in the urine with the remaining 21 % in the faeces. Moreover, the parent compound, donepezil, is the predominant elimination product in urine.

Plasma donepezil concentrations decline with a half life of approximately 70 hours.

Sex, race, and smoking history have no clinically significant influence on the plasma concentrations of donepezil hydrochloride.

Special populations

Patients with hepatic impairment

Patients with mild to moderate hepatic impairment have increased donepezil steady state concentrations; mean AUC by 48 % and mean C_{max} by 39 %.

Elderly:

The pharmacokinetics of donepezil has not been formally studied in healthy elderly subjects or in Alzheimer's or vascular dementia patients. However mean plasma levels in patients closely agreed with those of young healthy volunteers.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Aspartame
- Croscarmellose sodium
- Lactose monohydrate (spray dried)
- Magnesium stearate
- Microcrystalline cellulose
- Monosodium citrate anhydrous
- Polacrilin potassium
- Silica (colloidal anhydrous)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store in the original container at or below 30 °C.

6.5 Nature and contents of container

DONECEPT ODT 5 and 10 mg orally disintegrating tablets are packed in transparent PVC/PCTFE/ Aluminum blisters or Aluminum/ Aluminum blisters, which are subsequently packed into cardboard boxes.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD

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8. REGISTRATION NUMBER(S)

DONECEPT ODT 5: 53/5.3/0046

DONECEPT ODT 10: 53/5.3/0047

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 February 2021

10. DATE OF REVISION OF THE TEXT

02 March 2023