PROFESSIONAL INFORMATION FOR DONEPEZIL UNICORN 5 AND 10

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

DONEPEZIL UNICORN 5 (5 mg, film coated tablet)

DONEPEZIL UNICORN 10 (10 mg, film coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each DONEPEZIL UNICORN 5 film coated tablet contains 5 mg donepezil hydrochloride.

Contains sugar: lactose monohydrate 96,00 mg.

Each DONEPEZIL UNICORN 10 film coated tablet contains 10 mg donepezil hydrochloride.

Contains sugar: lactose monohydrate 192,00 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

DONEPEZIL UNICORN 5**:** White, round, biconvex, film coated tablet with D5 debossed on one side and plain on the other side.

DONEPEZIL UNICORN 10**:** Yellow, round, biconvex, film coated tablet with D10 debossed on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DONEPEZIL UNICORN is indicated for the symptomatic treatment of mild or moderate dementia in Alzheimer's disease.

4.2 Posology and method of administration

Adults/elderly:

The initial dosage is 5 mg once daily. Although a higher dose of 10 mg did not provide a statistically significant greater clinical benefit than the 5 mg dose, a daily dose of 10 mg may provide additional benefit for some patients. After 4 – 6 weeks, when steady-state concentrations of donepezil hydrochloride are achieved, the clinical response of the patient should be assessed and the dosage can be increased if necessary to a maximum daily dosage of 10 mg once daily. DONEPEZIL UNICORN should be taken in the evening.

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

Renal and hepatic impairment:

The clearance of DONEPEZIL UNICORN is not affected by renal or mild hepatic impairment. No dosage adjustments are required.

4.3 Contraindications

DONEPEZIL UNICORN is contraindicated in:

- Patients with known hypersensitivity to donepezil hydrochloride, piperidine derivatives, or to any of the inactive ingredients of DONEPEZIL UNICORN (see section 6.1).
- Pregnancy and lactation (see section 4.6).
- Children.
- Patients recovering from bladder or gastrointestinal surgery.

4.4 Special warnings and precautions for use

The supervision of an experienced doctor in the diagnosis and treatment of Alzheimer's dementia is required when treatment is commenced. Maintenance treatment can be continued for as long as a therapeutic benefit for the patient exists. It is important to reassess the clinical benefit of DONEPEZIL UNICORN on a regular basis. If evidence of a therapeutic effect is no longer present, DONEPEZIL UNICORN should be discontinued. The individual response of patients to DONEPEZIL UNICORN cannot be predicted.

The use of DONEPEZIL UNICORN 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.

Cardiovascular conditions:

Cardiovascular conditions, such as sick sinus syndrome, supraventricular conduction problems e.g. sinoatrial or atrioventricular block and unexplained syncopal episodes:

Cholinesterase inhibitors such as DONEPEZIL UNICORN may have vagotonic effects on heart rate (e.g. bradycardia). Syncopal episodes have been reported in association with the use of DONEPEZIL UNICORN.

There have been post-marketing reports of QTc interval prolongation and torsades de pointes (see sections 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 (electrocardiogram [ECG]) may be required.

Surgery:

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

Peptic ulcer disease or history thereof:

DONEPEZIL UNICORN may be expected to increase gastric acid secretion due to increased cholinergic activity. Patients should thus be monitored closely for symptoms of gastrointestinal bleeding especially those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs).

Genitourinary:

DONEPEZIL UNICORN may cause bladder outflow obstruction.

Seizures, history thereof and Parkinson's disease:

DONEPEZIL UNICORN may cause generalised convulsions.

Asthma, history thereof or chronic obstructive pulmonary disease:

DONEPEZIL UNICORN may aggravate these conditions due to the cholinomimetic actions. The administration of DONEPEZIL UNICORN concomitantly with other inhibitors of acetylcholinesterase, agonists or antagonists of the cholinergic system should be avoided (see section 4.5).

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 have 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 or presents with unexplained high fever without additional clinical manifestations of NMS, treatment with DONEPEZIL UNICORN should be discontinued.

Severe hepatic impairment

There is no known effect in patients with severe hepatic impairment.

Lactose warning:

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

Anticholinergics:

Because of the mechanism of action of DONEPEZIL UNICORN, it has the potential to interfere with the activity of anticholinergic medicines.

Cholinergic agonists and other cholinesterase inhibitors:

A synergistic effect may be expected when DONEPEZIL UNICORN is 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.

Nonsteroidal anti-inflammatory drugs (NSAIDs):

DONEPEZIL UNICORN may increase gastric acid secretion due to the increased cholinergic activity, and patients should be monitored for symptoms of active or occult gastrointestinal bleeding.

Cases of QTc interval prolongation and torsades de pointes have been reported for donepezil, as in DONEPEZIL UNICORN. Caution is advised when DONEPEZIL UNICORN is used in combination with other medicines known to prolong the QTc interval and clinical monitoring (electrocardiogram [ECG] may be required.

Examples include:

- Class IA antiarrhythmics (e.g. 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)

Medicines that induce the isoenzymes CYP2D6 and CYP3A4:

Carbamazepine, dexamethasone, phenobarbitone, phenytoin, rifampicin and alcohol may increase the rate of elimination of DONEPEZIL UNICORN.

Medicines highly bound to plasma proteins:

Although DONEPEZIL UNICORN is highly bound to plasma proteins (96 %), no displacement interactions were observed with furosemide, digoxin and warfarin. The metabolism of donepezil is not affected by concurrent administration of digoxin,

cimetidine, thioridazine, risperidone or sertraline. In vitro studies have shown that the cytochrome P450 enzymes 3A4 and to a minor extent 2D6 are involved in the metabolism of donepezil. Ketoconazole and quinidine, inhibitors of CYP3A4 and 2D6 respectively may inhibit donepezil metabolism.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safe use of DONEPEZIL UNICORN in pregnancy and lactation has not been established.

The potential risk for humans is unknown.

DONEPEZIL UNICORN should not be used during pregnancy.

Breastfeeding

The safety of DONEPEZIL UNICORN in lactation has not been established.

Donepezil is excreted in the milk of rats. It is not known whether donepezil is excreted in human breast milk and there are no studies in lactating women. Therefore, women on DONEPEZIL UNICORN should not breastfeed.

Fertility

There are no data on the effect of DONEPEZIL UNICORN.

4.7 Effects on ability to drive and use machines

DONEPEZIL UNICORN can affect the ability to drive a vehicle and to perform skilled tasks, such as operating machinery. Caution should be exercised.

4.8 Undesirable effects

Tabulated summary of adverse reactions

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

MedDRA system organ class	**Frequency**	**Side effects**
Infections and infestations	Frequent	Cold, influenza.
Blood and lymphatic system disorders	Less frequent	Ecchymosis.
	Frequency unknown	Haemolytic anaemia.
Metabolism and nutrition disorders	Frequent	Anorexia.
	Less frequent	Dehydration.
	Frequency unknown	Hyponatraemia.
Psychiatric disorders	Frequent	Agitation
	Less frequent	Mental depression
	Frequency unknown	Neuroleptic malignant syndrome, convulsions, hallucinations, confusion.
Nervous system disorders	Frequent	Insomnia, fatigue, agitation.
	Less frequent	Vertigo, dizziness, ataxia, abnormal dreams, headache, somnolence, syncope, aphasia, paraesthesia,

		tremor, mood or mental changes including abnormal crying, aggression, delusions, irritability, nervousness or restlessness.
Eye disorders	Less frequent	Cataract, eye irritation, blurred vision.
Cardiac disorders	Less frequent	Angina, bradycardia, atrial fibrillation.
	Frequency unknown	Sino-atrial block, atrioventricular block, Polymorphic ventricular tachycardia including Torsades de Pointes: electrocardiogram QT interval prolonged.
Vascular disorders	Less frequent	Vasodilation and hot flushes, hypertension or hypotension.
Respiratory, thoracic and mediastinal disorders	Less frequent	Bronchitis, upper respiratory tract infections, influenza, dyspnoea, pharyngitis.
Gastrointestinal disorders	Frequent	Nausea, diarrhoea, vomiting, dyspepsia.
	Less frequent	Peptic ulcers, constipation, weight loss, bloating, epigastric pain, faecal incontinence, gastrointestinal bleeding.
	Frequency unknown	Cholecystitis, abdominal pain.
Hepato-biliary disorders	Frequency unknown	Pancreatitis, hepatitis.

Skin and subcutaneous tissue disorders	Less frequent	Pruritus, diaphoresis, urticaria, ecchymoses.
	Frequency unknown	Rash.
Musculoskeletal, connective tissue and bone disorders	Frequent	Muscle cramps.
	Less frequent	Arthritis, bone fracture.
Renal and urinary disorders	Less frequent	Frequent urination, urinary tract infections, urinary incontinence, nocturia.
Reproductive system and breast disorders	Less frequent:	Increased libido.
General disorders and administrative site conditions	Less frequent:	Pain including chest pain, toothache.
Investigations	Frequency unknown	Minor changes in serum concentrations of creatine 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 or directly to Unicorn Pharmaceuticals (Pty) Ltd. at vigilance@unicornpharma.co.za.

4.9 Overdose

Overdosage with DONEPEZIL UNICORN can result in cholinergic crisis characterised by bradycardia, hypotension, severe nausea, vomiting, salivation, sweating, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.

Treatment is symptomatic and supportive. Tertiary anticholinergics, such as atropine, may be used as an antidote for DONEPEZIL UNICORN overdosage. Intravenous atropine sulphate titrated to effect is recommended; initially, a dose of 1,0 to 2,0 mg IV, with subsequent doses based upon clinical response. It is not known whether donepezil hydrochloride and/or its metabolites can be removed by dialysis (haemodialysis, peritoneal dialysis or haemofiltration).

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 5.3 Cholinomimetics (cholinergics)

Pharmacotherapeutic group: Anti-dementia drugs; anticholinesterases

ATC code: N06DA02

5.1 Pharmacodynamic properties:

Donepezil hydrochloride is a specific non-competitive reversible inhibitor of acetylcholinesterase (AChE) and appears to exert its therapeutic effect in Alzheimer’s

patients by enhancing cholinergic function. Donepezil hydrochloride exhibits a relatively high degree of selectivity for neuronal AChE, at relative clinical doses. It has only weak inhibitory effects on butyrylcholinesterase (pseudocholinesterase), an enzyme which is widely distributed in the plasma and peripheral tissues.

As the dementia progresses, fewer cholinergic neurons are thought to remain functionally intact, and the effects of donepezil may be lessened.

The inhibition of acetylcholinesterase (AChE) in red blood cells by donepezil hydrochloride corresponds closely to its effect at synapses in the central nervous system (CNS). AChE inhibition in red blood cells has been used as an indicator of the clinical efficacy of donepezil in Alzheimer's disease patients.

The enzyme AChE occurs peripherally in red blood cells; therefore, measurement of AChE activity in erythrocyte membranes provides an index for donepezil hydrochloride pharmacodynamics.

There is no evidence that donepezil alters the course of the underlying process.

5.2 Pharmacokinetic properties:

Absorption:

Donepezil is well absorbed after oral administration with a relative bioavailability of 100 %. The rate and extent of absorption is not influenced by food intake or the time of administration. Time to peak plasma concentrations is between 3 to 4 hours.

Pharmacokinetics are linear over a dosage range of 1 to 10 mg given once a day. Following multiple-dose administration, donepezil accumulates in plasma by fourfold to

sevenfold, and steady-state is reached within 15 days with a mean plasma concentration of 14,2 ng/ml at steady-state.

Distribution:

The steady-state volume of distribution is 12 l/kg. Donepezil hydrochloride is approximately 96 % bound to human plasma proteins.

Metabolism/elimination:

Donepezil hydrochloride is extensively metabolised and undergoes first pass metabolism to four major metabolites, two of which are known to be active. Donepezil is metabolised by cytochrome P450 isoenzymes CYP2D6 and CYP3A4 and undergoes glucuronidation. The elimination is renal and biliary and the elimination half-life is approximately 70 hours.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium,

Lactose monohydrate,

Magnesium stearate,

Microcrystalline cellulose,

Opadry (macrogol, polyvinyl alcohol, talc, titanium dioxide).

Yellow iron oxide (colourant)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Donepezil Unicorn 5 and 10 is packed in transparent PVC/PVDC/silver aluminium foil blister strips of 10 tablets each.

30 tablets packed into an outer carton.

6.6 Special precautions for disposal and other handling

No special requirements

7. Holder of Certificate of Registration

Unicorn Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBERS

DONEPEZIL UNICORN 5: 46/5.3/0406

DONEPEZIL UNICORN 10**:** 46/5.3/0407

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09 June 2016

10. DATE OF REVISION OF THE TEXT

25 April 2024