Proposed professional information for NEPIZEL 5 & 10

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

NEPIZEL 5 mg film-coated tablets

NEPIZEL 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each NEPIZEL 5 film-coated tablet contains 5 mg donepezil hydrochloride.

Each NEPIZEL 10 film-coated tablet contains 10 mg donepezil hydrochloride.

Excipients with known effect

Contains sugar.

NEPIZEL 5: Each film-coated tablet contains 98 mg lactose monohydrate.

NEPIZEL 10: Each film-coated tablet contains 192 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

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

NEPIZEL 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

NEPIZEL 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 dosages of NEPIZEL 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.

NEPIZEL 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 NEPIZEL to be achieved. Following a one-month clinical assessment of treatment at 5 mg/day, the dose of NEPIZEL 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 NEPIZEL 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 NEPIZEL is not affected by these conditions.

4.3 Contraindications

- Hypersensitivity to donepezil hydrochloride, piperidine derivatives, or to any of the excipients of

NEPIZEL (see section 6.1).

- Pregnancy and lactation (see section 4.6).
- Safety and efficacy of NEPIZEL have not been established in children, therefore it is not recommended for use in 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 NEPIZEL on a regular basis. If evidence of a therapeutic effect is no longer present, NEPIZEL should be discontinued. The individual response of patients to NEPIZEL cannot be predicted.
The use of NEPIZEL 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

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

Cardiovascular conditions

Because of their pharmacological action, cholinesterase inhibitors, such as NEPIZEL, 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.

There have been reports of syncope and seizures. In investigating such patients, the possibility of heart block or long sinusal pauses should be considered.

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, bradydysrhythmias), or electrolyte disturbances (hypokalaemia, hypomagnesaemia). Clinical monitoring (electrocardiogram [ECG]) may be required.

Gastrointestinal conditions

NEPIZEL 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 at increased risk for developing ulcers, e.g. those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs). However, the clinical studies with donepezil, as in NEPIZEL, showed no increase relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Genitourinary

Cholinomimetics, including NEPIZEL, may cause bladder outflow obstruction.

Neurological conditions

NEPIZEL is 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 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 NEPIZEL 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 NEPIZEL concomitantly with other inhibitors of acetylcholinesterase, agonists or antagonists of the cholinergic system should be avoided (see section 4.5).

Severe hepatic impairment

There are no data for patients with severe hepatic impairment.

Lactose warning

NEPIZEL contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take NEPIZEL.

4.5 Interaction with other medicines and other forms of interaction

Medicines highly bound to plasma proteins

Although NEPIZEL is highly bound to plasma proteins (96 %) no displacement interactions were observed with furosemide, digoxin and warfarin.

Effect of NEPIZEL on the metabolism of other medicines

NEPIZEL 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, NEPIZEL 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 NEPIZEL

The metabolism of donepezil hydrochloride is not affected by concurrent administration of digoxin, cimetidine, thioridazine, risperidone or sertraline. *In vitro* studies have shown that the cytochrome P450 isoenzymes 3A4 and to a minor extent 2D6 are involved in the metabolism of donepezil. Medicine interaction studies performed *in vitro* show that ketoconazole and quinidine, inhibitors of CYP3A4 and 2D6 respectively, inhibit donepezil metabolism. Therefore these and other CYP3A4 inhibitors, such as itraconazole and erythromycin, and CYP2D6 inhibitors, such as fluoxetine could inhibit the metabolism of NEPIZEL. In healthy volunteers, ketoconazole increased mean donepezil concentrations by about 30 %.

Enzyme inducers, such as rifampicin, phenytoin, carbamazepine, dexamethasone, phenobarbital and alcohol may increase the rate of elimination of NEPIZEL. Since the magnitude of an inhibiting or inducing effect is unknown, such medicine combinations should be used with care.

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

There is also the potential for synergistic activity with concomitant treatment involving medications such as succinylcholine, other neuromuscular blocking medicines or cholinergic agonists, or beta blocking medicines that have effects on cardiac conduction.

Nonsteroidal anti-inflammatory drugs (NSAIDs):

NEPIZEL 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 NEPIZEL. Caution is advised when NEPIZEL 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).

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of NEPIZEL in pregnancy has not been established.

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

NEPIZEL should not be used during pregnancy.

Breastfeeding

The safety of NEPIZEL 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 in lactating women. Therefore, women on NEPIZEL should not breastfeed.

Fertility

There are no data on the effect of NEPIZEL 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 machines. Furthermore, NEPIZEL can cause side-effects, such as fatigue, dizziness and muscle cramps, mainly when initiating or increasing the dose. The treating doctor should routinely evaluate the ability of patients on NEPIZEL to continue driving or operating complex machines.

4.8 Undesirable effects

The most frequent adverse events are diarrhoea, muscle cramps, fatigue, nausea, vomiting and insomnia.

The following side effects have been reported:

Infections and infestations

Frequent: Common cold, influenza.

Blood and the lymphatic system disorders

Frequency unknown: Haemolytic anaemia.

Metabolism and nutrition disorders

Frequent: Anorexia.

Less frequent: Dehydration.

Frequency unknown: Hyponatraemia.

Psychiatric disorders

Frequent: Hallucinations**, agitation**, aggressive behaviour**, abnormal dreams and nightmares**, delusions, depression.

Less frequent: Abnormal crying, irritability, nervousness, restlessness, confusion.

Nervous system disorders

Frequent: Syncope*, headache, dizziness, insomnia, somnolence.

Less frequent: Seizure*, extrapyramidal symptoms, neuroleptic malignant syndrome, ataxia, aphasia, paraesthesia, tremor, mood or mental changes.

Eye disorders

Less frequent: Cataract, eye irritation, blurred vision.

Ear and labyrinth disorders

Less frequent: Vertigo.

Cardiac disorders

Less frequent: Angina, bradycardia, atrial fibrillation, sino-atrial block, atrioventricular block.

Frequency unknown: Polymorphic ventricular tachycardia including torsades de pointes, electrocardiogram QT interval prolonged.

Vascular disorders

Less frequent: Vasodilation, hot flushes, hypertension, hypotension.

Respiratory, thoracic and mediastinal disorders

Less frequent: Bronchitis, upper respiratory tract infections, dyspnoea, pharyngitis.

Gastrointestinal disorders

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

Less frequent: Gastrointestinal haemorrhage, gastric and duodenal ulcers, salivary hypersecretion, constipation, bloating, epigastric pain, toothache.

Frequency unknown: Cholecystitis, abdominal pain.

Hepatobiliary disorders

Less frequent: Liver dysfunction including hepatitis***.

Frequency unknown: Pancreatitis.

Skin and subcutaneous tissue disorders

Less frequent: Rash, pruritus, diaphoresis, ecchymosis urticaria.

Musculoskeletal, connective tissue and bone disorders

Frequent: Muscle cramps.

Less frequent: Rhabdomyolysis****, arthritis.

Renal and urinary disorders

Frequent: Urinary incontinence, frequent urination.

Less frequent: Urinary tract infections, nocturia.

Reproductive system and breast disorders

Less frequent: Increased libido.

General disorders and administrative site conditions

Frequent: Fatigue, pain.

Less frequent: Chest pain.

Investigations

Frequent: Weight decrease.

Less frequent: Minor increase in serum concentrations of muscle creatine kinase.

Injury and poisoning

Frequent: Accidents including falls, bone fracture.

* In investigating patients for syncope or seizure the possibility of heart block or long sinusal pauses should be considered (see section 4.4).

** Reports of hallucinations, abnormal dreams, nightmares, agitation and aggressive behaviour have resolved on dose reduction or discontinuation of treatment.

*** In cases of unexplained liver dysfunction, withdrawal of NEPIZEL should be considered.

**** Rhabdomyolysis has been reported to occur independently of neuroleptic malignant syndrome and in close temporal association with NEPIZEL initiation or dose increase.

The frequency of these adverse events may be affected by rate of the dose titration of NEPIZEL.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of NEPIZEL is important. It allows continued monitoring of the benefit/risk balance of NEPIZEL. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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 NEPIZEL 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.

General supportive measures should be utilised. Tertiary anticholinergics, such as atropine may be used as an antidote for NEPIZEL overdosage. Intravenous (IV) 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. 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 hemofiltration).

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 and reversible inhibitor of acetylcholinesterase (AChE), the predominant cholinesterase in the brain. Donepezil hydrochloride is *in vitro* over 1 000 times more potent an inhibitor of this enzyme than of butyrylcholinesterase, an enzyme that is present mainly outside the central nervous system.

The inhibition of acetylcholinesterase (AChE) in red blood cells by donepezil hydrochloride corresponds closely to its effects in the cerebral cortex and has been shown to correlate to changes in ADAS-cog, a sensitive and well validated scale that examines cognitive performance – including memory, orientation, attention, reason, language and praxis. 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

Maximum plasma levels are reached approximately 3 to 4 hours after oral 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 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.
Donepezil is well absorbed after oral administration with a relative bioavailability of 100 %.
Neither food nor time of administration (morning versus evening dose) affects the absorption of donepezil hydrochloride.
Pharmacokinetics are linear over a dosage range of 1 to 10 mg given once a day.

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 hydrochloride is hepatically metabolised by the cytochrome P450 system-to multiple metabolites. 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**.**

Elimination

The predominant route for the elimination of both the parent compound and its metabolites is renal. Following administration of a single 5 mg dose of ^{14}C-labelled donepezil hydrochloride, approximately 57 % of the total administered radioactivity was recovered from the urine (17 % as unchanged donepezil), and 14,5 % was recovered from the faeces, suggesting biotransformation and urinary excretion as the primary routes of elimination. Moreover, the parent compound, donepezil, is the predominant elimination product in urine.

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

Special populations

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.

Sex, race and smoking

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Film coating:

Macrogol

Talc

Titanium dioxide (E171) (colourant)

NEPIZEL 10 also contains iron oxide yellow (E172) (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 the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

Transparent PVC/PVDC/silver aluminium foil blister strips of 10 tablets each, packed into an outer carton.

Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unichem SA (Pty) Ltd

San Domenico, Ground Floor, Unit 4

10 Church Street, Durbanville

Cape Town

7551

8. REGISTRATION NUMBERS

NEPIZEL 5: 46/5.3/0404

NEPIZEL 10: 46/5.3/0405

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09 June 2016

10. DATE OF REVISION OF THE TEXT

05 June 2023