PROFESSIONAL INFORMATION FOR ALZIDO 5 mg / 10 mg

SCHEDULING STATUS: S5

PROPRIETARY NAME (and dosage form):

ALZIDO 5 mg (film coated tablets)

ALZIDO 10 mg (film coated tablets)

COMPOSITION

Active ingredient

Each **ALZIDO 5 mg** film coated tablet contains 5 mg donepezil hydrochloride

Each **ALZIDO 10 mg** film coated tablet contains 10 mg donepezil hydrochloride

Inactive ingredients

Hydroxypropylcellulose, maize starch, magnesium stearate, microcrystalline cellulose, Opadry White (containing hypromellose, titanium dioxide, macrogol and talc).

Contains lactose monohydrate.

PHARMACOLOGICAL CLASSIFICATION

A 5.3 Cholinomimetics (cholinergics)

PHARMACOLOGICAL ACTION

Pharmacodynamics

Donepezil hydrochloride is a reversible inhibitor of acetylcholinesterase (AChE), the predominant cholinesterase in the brain. Donepezil inhibits AchE a 1000 times more than butyrylcholinesterase, an enzyme which is present mainly outside the central nervous system (CNS). Donepezil appears to exert its therapeutic effect by enhancing cholinergic function.

The inhibition of AChE in red blood cells by donepezil corresponds closely to its effect in the cerebral cortex. The enzyme AChE occurs peripherally in red blood cells; therefore measurement of AChE activity in erythrocyte membranes provides an index for donepezil pharmacodynamics.

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

Pharmacokinetics

Absorption:

Oral administration of donepezil produces predictable plasma concentrations. Time to peak plasma concentrations is between 3 to 4 hours.

Plasma concentrations and area under the curve rise proportionally to the dose. 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.

Neither food nor time of administration affects the absorption of donepezil.

Distribution:

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

Metabolism/Elimination:

Donepezil is hepatically metabolised and the predominant route for the elimination of both the parent substance and its metabolites is renal. 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). The elimination half-life is approximately 70 hours.

INDICATIONS

ALZIDO is indicated for the symptomatic treatment of mild to moderate dementia in Alzheimer's disease.

CONTRAINDICATIONS

- Patients with a known hypersensitivity to donepezil hydrochloride, piperidine derivatives or to any of the ingredients used in the formulation (see **COMPOSITION**).
- Pregnancy and lactation (see **PREGNANCY AND LACTATION**).
- Children and adolescents under the age of 18 years.
- Patients recovering from bladder or gastrointestinal surgery.

WARNINGS

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. It is important to reassess the clinical benefit of **ALZIDO** on a regular basis.

If evidence of a therapeutic effect is no longer present, **ALZIDO** should be discontinued. The individual response of patients to **ALZIDO** cannot be predicted.

The use of **ALZIDO** 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.

Surgery: **ALZIDO**, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia.

Cardiovascular condition, such as sick sinus syndrome, supraventricular conduction problems e.g. sinoartrial or artrioventricular block and unexplained syncopal episodes: **ALZIDO** may have vagotonic effects on heart rate (e.g. bradycardia). Syncopal episodes have been reported in association with the use of **ALZIDO**.

Peptic ulcer disease or history of: **ALZIDO** 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 non-steroidal anti-inflammatory drugs (NSAIDs).

Genitourinary: **ALZIDO** may cause bladder outflow obstruction.

Neurological conditions: **ALZIDO** may have some potential to cause generalised convulsions. However, seizure activity may also be a manifestation of Alzheimer's disease.

Asthma, history of or chronic obstructive pulmonary disease: **ALZIDO** may aggravate these conditions due to the cholinomimetic actions. The administration of **ALZIDO** concomitantly with other inhibitors of acetylcholinesterase, agonists or antagonists of the cholinergic system should be avoided.

INTERACTIONS:

Anticholinergics: Because of the mechanism of action, **ALZIDO** has the potential to interfere with the activity of anticholinergic medications.

Cholinergic agonists and other cholinesterase inhibitors: A synergistic effect may be expected when **ALZIDO** 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.

Non-steroidal anti-inflammatory drugs (NSAIDs): **ALZIDO** may increase gastric acid secretion due to the increased cholinergic activity and patients should be monitored for symptoms of active or occult gastrointestinal bleeding.

Medicines that induce the isoenzymes CYP2D6 and CYP3A4: Carbamazepine, dexamethasone, phenobarbital, phenytoin, alcohol and rifampicin may increase the rate of elimination of **ALZIDO**.

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

*Effects of other medicines on the metabolism of **ALZIDO**:* Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro*. Therefore these and other CYP3A4 inhibitors, such as itraconazole, erythromycin and CYP2D6 inhibitors such as fluoxetine could inhibit the metabolism of donepezil.

PREGNANCY AND LACTATION

The safe use of **ALZIDO** in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

Adults/Elderly:

The initial dosage is 5 mg once daily. Although a higher dose of 10 mg does 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.

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

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

Renal and hepatic impairment:

The clearance of **ALZIDO** is not affected by renal or mild to moderate hepatic impairment.

No dosage adjustments are required.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side effects

Blood and the lymphatic system disorders

The following side effect has been reported but the frequency is unknown:

Haemolytic anaemia

Metabolism and nutrition disorders

Frequent: Anorexia

Less frequent: Dehydration

The following side effect has been reported but the frequency is unknown:

Hyponatraemia

Psychiatric disorders

Frequent: Hallucinations, insomnia, agitation, abnormal dreams, delusions

Less frequent: Depression, mood or mental changes including abnormal crying, aggression, irritability, nervousness, restlessness

The following side effect has been reported but the frequency is unknown:

Confusion

Nervous system disorders

Frequent: Fatigue, dizziness, headache, somnolence

Less frequent: Ataxia, syncope, aphasia, paraesthesia, tremor, neuroleptic malignant syndrome, convulsions

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

Vascular disorders

Less frequent: Vasodilation, hot flushes, hypertension, hypotension

Respiratory, thoracic and mediastinal disorders

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

Gastrointestinal disorders

Frequent: Nausea, diarrhoea, vomiting, dyspepsia, weight loss, faecal incontinence, abdominal disturbance

Less frequent: Peptic ulcers, constipation, bloating, epigastric pain, gastrointestinal bleeding, toothache, duodenal ulcer, gastric ulcer, pancreatitis

The following side effect has been reported but the frequency is unknown:

Cholecystitis

Hepato-biliary disorders

Less frequent: Hepatitis

Skin and subcutaneous tissue disorders

Frequent: Sweating, rash

Less frequent: Pruritus, diaphoresis, urticaria, ecchymosis

Musculoskeletal, connective tissue and bone disorders

Frequent: Muscle cramps

Less frequent: Arthritis, bone fracture

Renal and urinary disorders

Frequent: Frequent urination.

Less frequent: Urinary tract infections, urinary incontinence, nocturia

Reproductive system and breast disorders

Less frequent: Increased libido

General disorders and administrative site conditions

Frequent: Pain including chest pain

Investigations

Less frequent: Minor changes in serum concentrations of creatinine kinase, increased liver transaminase

Injury, poisoning and procedural complications

Less frequent: Accident

Special precautions

The use of donepezil is associated with weight loss. Patients' weight should be monitored during treatment with **ALZIDO**.

Female patients are more susceptible to nausea, vomiting, anorexia and weight loss.

ALZIDO contains lactose and should not be given to patients with rare hereditary problems or a history of galactose intolerance, Lapp lactose deficiency or glucose-galactose malabsorption.

Effects on ability to drive and use machines

ALZIDO can affect the ability to drive or use machines. Caution should be exercised.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Overdosage with **ALZIDO** 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 **ALZIDO** 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 hemofiltration).

IDENTIFICATION

ALZIDO 5 mg: White to off white, round shaped, biconvex film coated tablets debossed with ‘ZF9’ on one side and plain on the other side.

ALZIDO 10 mg: White to off white, round shaped, biconvex film coated tablets debossed with ‘ZF10’ on one side and plain on the other side.

PRESENTATION

Clear PVDC/PVC/silver aluminium foil blister strips of 14 tablets each.

Two (2) blister strips of 14 tablets each are packed into an outer carton.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

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

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

ALZIDO 5 mg: 45/5.3/0939

ALZIDO 10 mg: 45/5.3/0940

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE

Zydus Healthcare SA (Pty) Ltd

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