SCHEDULING STATUS

S5

PROPRIETARY NAME (and dosage form)

CURLOVON 5 (film-coated tablet)

CURLOVON 10 (film-coated tablet)

COMPOSITION

CURLOVON 5

Each film-coated tablet contains donepezil hydrochloride 5 mg.

Contains sugar (lactose monohydrate).

Other ingredients are hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose and pre-gelatinised starch. The coating contains hypromellose, macrogol and titanium dioxide.

CURLOVON 10

Each film-coated tablet contains donepezil hydrochloride 10 mg.

Contains sugar (lactose monohydrate).

Other ingredients are hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose and pre-gelatinised starch. The coating contains hypromellose, iron oxide yellow, macrogol and titanium dioxide.

PHARMACOLOGICAL CLASSIFICATION

A 5.3 Cholinomimetics (cholinergics)

PHARMACOLOGICAL ACTION

Pharmacodynamics

Donepezil hydrochloride is a reversible inhibitor of acetylcholinesterase, the predominant cholinesterase in the brain.

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.

Pharmacokinetics

Absorption

Oral administration of **CURLOVON** 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) affects 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 distribution of donepezil hydrochloride in various body tissues has not been definitively studied. However, in a mass balance study conducted in healthy male volunteers, 240 hours after the administration of a single 5 mg dose of ^{14}C-labelled donepezil hydrochloride, approximately 28 % of the label remained unrecovered. This suggests that donepezil hydrochloride and/or any of its metabolites may persist in the body for more than 10 days. The average CSF:Plasma ratio for both doses, expressed as a percent of the concentration in plasma, was 15,7 %.

Metabolism/Excretion

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

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

INDICATIONS

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

CONTRAINDICATIONS

Hypersensitivity to donepezil hydrochloride, piperidine derivatives, or to any inactive ingredients used in the formulation.

Safety and efficacy of donepezil hydrochloride have not been established in children; therefore it is not recommended for use in children.

WARNINGS

Only a doctor, experienced in the treatment of Alzheimer's dementia, should initiate treatment. Maintenance treatment can be continued for as long as a therapeutic benefit for the patient exists.

Individual response to **CURLOVON** cannot be predicted. Therefore, the clinical benefit of **CURLOVON** should be reassessed on a regular basis. Discontinuation should be considered when evidence of a therapeutic effect is no longer present.

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

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

Cardiovascular Conditions: Due to their pharmacological action, cholinesterase inhibitors, such as **CURLOVON,** 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 have been reported in association

with the use of **CURLOVON**.

Gastrointestinal Conditions: **CURLOVON** may promote gastric acid production. 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 medicines (NSAIDS). Clinical studies with donepezil hydrochloride have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

CURLOVON, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhoea, nausea and vomiting. These effects, when they occur, appeared 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 **CURLOVON**.

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

Neurological Conditions: **CURLOVON** is believed to have some potential to cause generalised convulsions. However, seizure activity may also be a manifestation of Alzheimer's Disease.

Pulmonary Conditions: **CURLOVON** should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease.

The administration of **CURLOVON** concomitantly with other inhibitors of acetylcholinesterase, or with agonists or antagonists of the cholinergic system, should be avoided.

INTERACTIONS

Medicines Highly Bound to Plasma Proteins:

Medicine displacement studies have been performed *in vitro* between this highly bound medicine (96 %) and other medicines such as furosemide, digoxin and warfarin. **CURLOVON,** at concentrations of 0,3 to 10 µg/ml, did not affect the binding of furosemide (5 µg/ml), digoxin (2 µg/ml), and warfarin (3 µg/ml) to human albumin. Similarly, the binding of **CURLOVON** to human albumin was not affected by furosemide, digoxin and warfarin.

*Effect of **CURLOVON** on the Metabolism of Other Medicines:*

No *in vivo* clinical trials have investigated the effect of donepezil hydrochloride on the clearance of medicines metabolised by CYP3A4 (e.g. cisapride) or by CYP2D6 (e.g. imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean Ki about 50-130 µM). This indicates, given the therapeutic plasma concentrations of donepezil (164 µM), little likelihood of interference.

Whether donepezil hydrochloride has any potential for enzyme induction is not known. Donepezil hydrochloride and/or any of its metabolites do not inhibit the metabolism of theophylline, warfarin, cimetidine, digoxin, thioridazine, risperidone and sertraline in humans. In a study of Parkinson's disease patients on optimal treatment with levodopa/carbidopa, administration of donepezil hydrochloride for 21 days had no effects on levodopa or carbidopa blood levels. In this study no effects on motor activity were observed.

*Effect of Other Medicines on the Metabolism of **CURLOVON**:* Ketoconazole and quinidine, inhibitors of CYP450, CYP3A4 and CYP2D6, 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.

In a study in healthy volunteers, ketoconazole increased mean donepezil concentrations by 30 %. These increases are smaller than those produced by ketoconazole for other agents sharing the CYP3A4 pathway and are not likely to be clinically relevant. Administration of donepezil had no effect on the pharmacokinetics of ketoconazole. Inducers of CYP2D6 and CYP3A4 (e.g. phenytoin, carbamazepine, alcohol, dexamethasone, rifampicin and phenobarbital) could increase the rate of elimination of donepezil hydrochloride.

Formal pharmacokinetic studies demonstrated that the metabolism of donepezil hydrochloride is not significantly affected by concurrent administration of digoxin, cimetidine, risperidone or sertraline.

Use with anticholinergics:

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

Use with Cholinomimetics and other Cholinesterase Inhibitors:

A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine.

PREGNANCY AND LACTATION

CURLOVON is not recommended in pregnancy and lactation as safety has not been established.

DOSAGE AND DIRECTIONS FOR USE

The established effective dosages of **CURLOVON** is 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 is initiated at 5 mg/day (once-a-day dosing).

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 donepezil hydrochloride to be achieved.

Following a one-month clinical assessment of treatment at 5 mg/day, the dose of **CURLOVON** 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.

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 donepezil hydrochloride is not affected by these conditions.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Side-effects

The side-effects reported with **CURLOVON** and their frequency, are listed below.

Infections and Infestations

Frequent: Common cold, influenza

Metabolism and nutrition disorders

Less frequent: Dehydration

Psychiatric disorders

Frequent: Abnormal dreams, agitation, delusions, depression, hallucinations, insomnia

Less frequent: Abnormal crying, aggressive behaviour, irritability, nervousness, restlessness, confusion

Reproductive system and breast disorders

Less frequent: Increased libido

Nervous system disorders

Frequent: Dizziness, headache, somnolence

Less frequent: Aphasia, ataxia, paraesthesia, syncope, tremor, seizure, extrapyramidal symptoms

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, angina pectoris

Vascular disorders

Less frequent: Hot flushes, hypertension, hypotension, vasodilation

Respiratory, thoracic and mediastinal disorders

Less frequent: Dyspnoea, sore throat

Gastrointestinal disorders

Frequent: Abdominal disturbance, anorexia, diarrhoea, faecal incontinence, nausea, vomiting, dyspepsia

Less frequent: Bloating, epigastric pain, gastrointestinal haemorrhage, toothache, duodenal ulcer, gastric ulcer

Hepato-biliary disorders

Less frequent: Hepatitis

Skin and subcutaneous tissue disorders

Less frequent: Diaphoresis, ecchymosis, pruritus, urticaria, rash

Musculoskeletal and connective tissue disorders

Frequent: Muscle cramps

Renal and urinary disorders

Frequent: Frequent urination

Less frequent: Nocturia, urinary incontinence

General disorders and administration site conditions

Frequent: Fatigue, pain, sweating

Less frequent: Chest pain

Investigations

Frequent: Weight decreases

Less frequent: Minor increases in serum concentrations of muscle creatine kinase

Injury, poisoning and procedural complications

Less frequent: Accidental falls, bone fractures

There is evidence to suggest that the frequency of these common adverse events may be affected by rate of dose titration.

Special precautions

CURLOVON should be used with caution, if at all, in patients with gastrointestinal or urinary-tract obstruction (see **Warnings).**

Care is also required in patients with a history of asthma, obstructive pulmonary disease, Parkinson's disease, or seizures, and in those with, or at risk of, developing, peptic ulcer disease. Patients with cardiovascular conduction disorders such as sick-sinus syndrome may be susceptible to the vagotonic effects of **CURLOVON (s**ee **Warnings -** section under **Cardiovascular, Gastrointestinal, Genitourinary and Pulmonary conditions).**

CURLOVON contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption, should not take **CURLOVON**.

Effects on ability to drive and use machines:

Dementia may cause impairment of driving performance or compromise the ability to use machinery. Furthermore, **CURLOVON** can induce fatigue, dizziness and muscle cramps,

mainly when initiating or increasing the dose. The treating medical doctor should routinely evaluate the ability of patients on **CURLOVON** to continue driving or operating complex machines.

Known symptoms of overdosage and particulars of its treatment

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 **CURLOVON** 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 **CURLOVON** overdosage. Intravenous atropine sulphate titrated to effect is recommended: An 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).

IDENTIFICATION

CURLOVON 5: White round, biconvex, film-coated tablets debossed ‘DNP’ on one side and ‘5’ on the other side.

CURLOVON 10: Yellow, round, biconvex, bevel-edged film-coated tablets debossed ‘DNP’ on one side and ‘10’ on the other side.

PRESENTATION

CURLOVON 5: 14/30/60/90/120 film-coated tablets in white HDPE containers with white plastic caps, and with a non-woven fabric paper pouch containing silica gel granules included as desiccant.
30 film-coated tablets in 3 strips of 10 film-coated tablets in clear, transparent PVC-Aclar/Alu and silvery coloured Alu/Alu blisters, packed in a carton box.

CURLOVON 10: 14/30/60/90/120 film-coated tablets in white HDPE containers with white plastic caps, and with a non-woven fabric paper pouch containing silica gel granules included as desiccant.
30 film-coated tablets in 3 strips of 10 film-coated tablets in clear, transparent PVC-Aclar/Alu and silvery coloured Alu/Alu blisters, packed in a carton box.

STORAGE INSTRUCTIONS

Store at or below or 25 °C.
Keep the blisters in the carton until required for use.
Keep the HDPE container tightly closed.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

CURLOVON 5: 44/5.3/0933
CURLOVON 10: 44/5.3/0934

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd
Third Floor, The Place
1 Sandton Drive
Sandton 2196

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