PROFESSIONAL INFORMATION

SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

ENSORIN 5 mg (film-coated tablet)

ENSORIN 10 mg (film-coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ENSORIN 5 mg: Each film-coated tablet contains 5 mg donepezil hydrochloride. Contains sugar: 87,9 mg lactose monohydrate.

ENSORIN 10 mg: Each film-coated tablet contains 10 mg donepezil hydrochloride. Contains sugar: 175,8 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ENSORIN 5 mg : White to off white, round shaped, biconvex, film coated tablets debossed with “ML 89” on one side and plain on the other side.

ENSORIN 10 mg : Yellow colour, round shaped, biconvex, film coated tablets debossed with “ML 88” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ENSORIN is indicated for the symptomatic treatment of mild to moderate Alzheimer's dementia.

4.2 Posology and method of administration

Posology

Adults/Elderly:

Treatment is initiated at 5 mg/day (once-a-day dosing). **ENSORIN** should be taken orally, in the evening, just prior to retiring. The 5 mg/day dose should be maintained for at least one month 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.

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.

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

Renal and hepatic impairment:

A similar dose schedule can be followed for patients with renal impairment, as clearance of **ENSORIN** is not affected by this condition.

Children:

ENSORIN is contra-indicated for use in children.

Method of administration

Oral use

4.3 Contraindications

- **ENSORIN** is contra-indicated in patients with a known hypersensitivity to donepezil hydrochloride, piperidine derivatives, or to any of the excipients listed in section 6.1.
- Children and adolescent under the age of 18 years.

4.4 Special warnings and precautions for use

Treatment should be initiated and supervised by a doctor experienced in the diagnosis and 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 **ENSORIN** should be reassessed on a regular basis. Discontinuation should be considered when evidence of a therapeutic effect is no longer present. Individual response to **ENSORIN** cannot be predicted.

Upon discontinuation of treatment, a gradual abatement of the beneficial effects of **ENSORIN** will occur.

The use of **ENSORIN** 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 investigated.

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

Cardiovascular Conditions: Because of its pharmacological action, **ENSORIN** 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 association with donepezil. In such patients, the possibility of heart block or long sinusal pauses should be considered.

Gastrointestinal Conditions: **ENSORIN** may promote gastric acid production. Patients at increased risk for developing ulcers, e.g. those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs), should be monitored for symptoms of active or occult gastrointestinal bleeding.

Donepezil, 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 donepezil.

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

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

ENSORIN may have the potential to exacerbate or induce extrapyramidal symptoms.

Pulmonary Conditions: Because of its cholinomimetic actions, **ENSORIN** should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease.

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

Patients recovering from bladder or gastrointestinal surgery: **ENSORIN** should be used with caution, if at all, in patients with gastrointestinal or urinary-tract obstruction; **ENSORIN** is not recommended in patients recovering from bladder or gastrointestinal surgery.

Severe Hepatic Impairment: There are no data for patients with severe hepatic impairment.

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

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

Female patients have been found to be more susceptible to nausea, vomiting, anorexia and weight loss.

Lactose intolerance:

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

4.5 Interaction with other medicines and other forms of interaction

ENSORIN and/or any of its metabolites do not inhibit the metabolism of theophylline, warfarin, cimetidine, digoxin, thioridazine, risperidone and sertraline in humans. The metabolism of **ENSORIN** is not affected by concurrent administration of digoxin or cimetidine. *In vitro* studies have shown that the cytochrome P450 isoenzymes 3A4 and to a minor extent 2D6 are involved in the metabolism of **ENSORIN**.

Interaction studies performed *in vitro* show that ketoconazole and quinidine, inhibitors of CYP3A4 and 2D6 respectively, inhibit **ENSORIN** metabolism.

Therefore, these and other CYP3A4 inhibitors, such as itraconazole and erythromycin, and CYP2D6 inhibitors, such as fluoxetine, could inhibit the metabolism of **ENSORIN**. In a study in healthy volunteers, ketoconazole increased mean donepezil concentrations by about 30 %.

These increases are smaller than those produced by ketoconazole for other agents sharing the CYP-3A4 pathway and are not likely to be clinically relevant.

Administration of **ENSORIN** would have no effect on the pharmacokinetics of ketoconazole.

Enzyme inducers, such as rifampicin, phenytoin, carbamazepine and alcohol may reduce the levels of **ENSORIN**. Since the magnitude of an inhibiting or inducing effect is unknown, such medicinal combinations should be used with care.

ENSORIN has the potential to interfere with medications having anticholinergic activity. There is also the potential for synergistic activity with concomitant treatment involving medications such as

succinylcholine, other neuro-muscular blocking agents or cholinergic agonists, such as bethanechol, or beta-blocking agents which have effects on cardiac conduction, but an *in vitro* study showed that donepezil had minimal effects on the hydrolysis of succinyl choline.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of **ENSORIN** in pregnancy has not been established.

Breastfeeding

The safety of **ENSORIN** in lactation has not been established.

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, **ENSORIN** can induce fatigue, dizziness and muscle cramps, mainly when initiating or increasing the dose. The treating doctor should routinely evaluate the ability of patients on **ENSORIN** to continue driving or operating complex machines.

4.8 Undesirable effects

Tabulated list of adverse reactions

MedDRA System organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequent	Common cold, influenza
	Less frequent	Urinary tract infections
Metabolism and nutrition disorders	Frequent	Anorexia
	Less frequent	Dehydration
Psychiatric disorders	Frequent	Hallucinations, agitation, aggressive behaviour, abnormal dreams, delusions, depression, insomnia

	Less frequent	Abnormal crying, increased libido, irritability, nervousness, restlessness
Nervous system disorders	Frequent	Syncope, dizziness, headache
	Less frequent	Seizure, aphasia, ataxia, paraesthesia, tremor, extrapyramidal symptoms, confusion
Eye disorders	Less frequent	Cataract, eye irritation, blurred vision
Ear and labyrinth disorders	Less frequent	Vertigo
Cardiac disorders	Less frequent	Bradycardia, sino-atrial block, atrioventricular block, angina
Vascular disorders	Less frequent	Hot flushes, hypertension, hypotension, vasodilation
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea, sore throat
Gastrointestinal disorders	Frequent	Diarrhoea, nausea, vomiting, abdominal disturbance, faecal incontinence
	Less frequent	Gastrointestinal haemorrhage, gastric and duodenal ulcers, bloating, epigastric pain, toothache
Hepato-biliary disorders	Less frequent	Hepatitis
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritis, sweating
	Less frequent	Diaphoresis, ecchymosis, urticaria
Musculoskeletal, connective tissue and bone disorders	Frequent	Muscle cramps
Renal and urinary disorders	Frequent	Urinary incontinence, frequent urination
	Less frequent	Nocturia

General disorders and administrative site conditions	Frequent	Fatigue, pain
	Less frequent	Chest pain
Investigations	Frequent	Weight decrease
	Less frequent	Minor increase in serum concentration of muscle creatine kinase, increased liver transaminases
Injury and poisoning	Frequent	Accident
	Less frequent	Bone fracture

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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to Macleods Pharmaceuticals SA (Pty) Ltd. at safety@macleodspharma.com.

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 **ENSORIN** 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 **ENSORIN** 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 **ENSORIN** and/or its metabolites can be removed by dialysis (haemodialysis, peritoneal dialysis, or haemofiltration).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 5.3 Cholinomimetics (cholinergics)

Pharmacodynamic properties

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 of butyrylcholinesterase, an enzyme that is present mainly outside the central nervous system.

Current theories on the pathogenesis of the cognitive signs and symptoms 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. There is no evidence that donepezil alters the course of the underlying dementing 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.

Food and time of administration does not affect the absorption of donepezil hydrochloride.

Distribution:

Donepezil hydrochloride is approximately 96 % bound to human plasma proteins. The plasma protein binding of the active metabolite 6-O-desmethyldonepezil is not known.

The distribution of donepezil hydrochloride in various body tissues has not been definitively studied.

Metabolism/Excretion:

Donepezil hydrochloride is both excreted in the urine intact and metabolised by the cytochrome P450 system to multiple metabolites.

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.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide, lactose monohydrate, microcrystalline cellulose, pregelatinised starch, magnesium stearate, hypromellose, titanium dioxide, talc, propylene glycol & yellow iron oxide (for 10mg only).

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 container closed tightly. The blister strips to be kept in the carton until required for use. Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

White HDPE bottles with white child resistant cap containing 30 or 90 tablets, as well as printed cartons with PVC/PVDC/Aluminium blister packs of 30 (3 strips x 10) or 100 (10 strips x 10) tablets.

Following minimum batch details is coded on Blister Strip and container:

Batch No. and Exp. Date.

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

GROUND FLOOR, BLOCK 1,

BASSONIA ESTATE OFFICE PARK (EAST),

1 CUSSONIA DRIVE,

BASSONIA ROCK EXT 12

ALBERTON

GAUTENG

8. REGISTRATION NUMBER:

ENSORIN 5 mg: 45/5.3/0682

ENSORIN 10 mg: 45/5.3/0683

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of registration: 06 March 2014

10. DATE OF REVISION OF THE TEXT

03 September 2024