Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Donesyn 5mg Orodispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 5 mg of Donepezil hydrochloride

Each 5 mg tablet contains 5.00 mg of aspartame and 124.69 mg lactose (spray dried).

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Orodispersible tablets.

White to off-white round, flat tablets, with bevelled edges, embossed with '5' on one side and plain on the other

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Donesyn tablets are indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia

4.2 Posology and method of administration

Oral Use
Adults/Elderly:

Treatment is initiated at 5 mg/day (once-a-day dosing). Donesyn should be taken orally, in the evening, just prior to retiring. The tablet should be placed on the tongue and allowed to disintegrate before swallowing with or without water, according to patient preference. 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. Following a one-month clinical assessment of treatment at 5 mg/day, the dose of donepezil hydrochloride 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.

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's dementia. Diagnosis should be made according to accepted guidelines (e.g. DSM IV, ICD 10). Therapy with donepezil should only be started if a caregiver is available who will regularly monitor drug intake for the patient. Maintenance treatment can be continued for as long as a therapeutic benefit for the patient exists. Therefore, the clinical benefit of donepezil should be reassessed on a regular basis. Discontinuation should be considered when evidence of a therapeutic effect is no longer present. Individual response to donepezil cannot be predicted.

Upon discontinuation of treatment, a gradual abatement of the beneficial effects of Donesyn is seen.

Renal impairment:

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

Hepatic impairment:

Due to possible increased exposure in mild to moderate hepatic impairment (see section 5.2), dose escalation should be performed according to individual tolerability. There are no data for patients with severe hepatic impairment.

Children and adolescents:

Donesyn is not recommended for use in children and adolescents below 18 years of age.

For doses not realisable/practicable with this strength other strengths of this medicinal product are available.

4.3 Contraindications

Hypersensitivity to the active substance, piperadine derivatives or to any of the excipients.

4.4 Special warnings and precautions for use

The use of donepezil 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: donepezil, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia.

Cardiovascular Conditions: Because of their pharmacological action, cholinesterase inhibitors 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.

Gastrointestinal Conditions: 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. However, the clinical studies with donepezil showed no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Genitourinary: Although not observed in clinical trials of donepezil, cholinomimetics may cause bladder outflow obstruction.

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

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 should be discontinued.

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

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 Donesyn concomitantly with other inhibitors of acetylcholinesterase, agonists or antagonists of the cholinergic system should be avoided.

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

This medicinal product contains aspartame E951 a source of phenylalanine. It may be harmful for people with phenylketonuria.
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Mortality in Vascular Dementia Clinical Trials

Three clinical trials of 6 months duration were conducted studying individuals meeting the NINDS-AIREN criteria for probable or possible vascular dementia (VaD). The NINDS_AIREN criteria are designed to identify patients whose dementia appears to be due solely to vascular causes and to exclude patients with Alzeimer's disease. In the first study, the mortality rates were 2/198 (1.0%) on donepezil hydrochloride 5 mg, 5/206 (2.4%) on donepezil hydrochloride 10 mg and 7/199 (3.5%) on placebo. In the second study, the mortality rates were 4/208 (1.9%) on donepezil hydrochloride 5 mg, 3/215 (1.4%) on donepezil hydrochloride 10 mg and 1/193 (0.5%) on placebo. In the third study, the mortality rates were 11/648 (1.7%) on donepezil 5 mg and 0/326 (0%) on placebo. The mortality rate for the three VaD studies combined in the donepezil hydrochloride group (1.7%) was numerically higher than in the placebo group (1.1%); however, this difference was not statistically significant. The majority of deaths in patents taking either donepezil hydrochloride or placebo appear to result from various vascular related causes, which could be expected in this elderly population with underlying vascular disease. An analysis of all serious non-fatal and fatal vascular events showed no difference in the rate of occurrence in the donepezil hydrochloride group relative to placebo.

In pooled Alzheimer's disease studies (n=4146), and when these Alzheimer's disease studies were pooled with other dementia studies including the vascular dementia studies (total n=6888), the mortality rate in the placebo groups numerically exceeded that in the donepezil hydrochloride groups.

4.5 Interaction with other medicinal products and other forms of interaction

Donepezil hydrochloride and/or any of its metabolites do not inhibit the metabolism of theophylline, warfarin, cimetidine or digoxin in humans. The metabolism of donepezil hydrochloride 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 donepezil. Drug 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 donepezil. In a study in healthy volunteers, ketoconazole increased mean donepezil concentrations by about 30%. Enzyme inducers, such as rifampicin, phenytoin, carbamazepine and alcohol may reduce the levels of donepezil. Since the magnitude of an inhibiting or inducing effect is unknown, such drug combinations should be used with care. Donepezil hydrochloride 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 or beta blocking agents that have effects on cardiac conduction.

4.6 Fertility, pregnancy and lactation

Pregnancy:
There are no adequate data from the use of donepezil in pregnant women.
Studies in animals have not shown teratogenic effect but have shown peri and post natal toxicity (see section 5.3). The potential risk for humans is unknown.
Donesyn should not be used during pregnancy unless clearly necessary.

Lactation:
Donepezil is excreted in the milk of rat. It is not known whether donepezil hydrochloride is excreted in human breast milk and there are no studies in lactating women. Therefore, women on donepezil should not breast feed.

4.7 Effects on ability to drive and use machines

Donesyn has minor or moderate influence on the ability to drive and use machines.

Dementia may cause impairment of driving performance or compromise the ability to use machinery. Furthermore, donepezil can induce fatigue, dizziness and muscle cramps, mainly when initiating or increasing the dose. The treating physician should routinely evaluate the ability of patients on donepezil to continue driving or operating complex machines.

4.8 Undesirable effects

The most common adverse events are diarrhoea, muscle cramps, fatigue, nausea, vomiting and insomnia.
Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency.

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10,000 to <1/1000)	Very rare (<1/10,000)
Infections and infestations		Common cold			
Metabolism and nutrition disorders		Anorexia			
Psychiatric disorders		Hallucinations** Agitation** Aggressive behaviour**			
Nervous system disorders		Syncope* Dizziness Insomnia	Seizure*	Extrapyramidal symptoms	Neuroleptic malignant syndrome
Cardiac disorders			Bradycardia	Sino-atrial block Atrioventricular block	
Gastrointestinal disorders	Diarrhoea Nausea	Vomiting Abdominal disturbance	Gastrointestinal haemorrhage Gastric and duodenal ulcers		
Hepato-biliary disorders				Liver dysfunction including hepatitis***	
Skin and subcutaneous tissue disorders		Rash Pruritis			
Musculoskeletal connective tissue and bone disorders		Muscle cramps			Rhabdomyolysis****
Renal and urinary disorders		Urinary incontinence			
General disorders and administration site disorders	Headache	Fatigue Pain			
Investigations			Minor increase in serum concentration		

			of muscle creatine kinase		
Injury and poisoning		Accident			

*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, agitation and aggressive behaviour have resolved on dose-reduction or discontinuation of treatment.

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

The estimated median lethal dose of donepezil hydrochloride following administration of a single oral dose in mice and rats is 45 and 32 mg/kg, respectively, or approximately 225 and 160 times the maximum recommended human dose of 10 mg per day. 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 cholinesterase inhibitors can result in cholinergic crisis characterized 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.

As in any case of overdose, general supportive measures should be utilised. Tertiary anticholinergics such as atropine may be used as an antidote for Donesyn 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).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The pharmacotherapeutic group: anti-dementia drugs; anticholinesterases; ATC-code N06DA02.

Donepezil hydrochloride is a specific and reversible inhibitor of acetylcholinesterase, the predominant cholinesterase in the brain. Donepezil hydrochloride is *in vitro* over 1000 times more potent an inhibitor of this enzyme than of butyrylcholinesterase, an enzyme that is present mainly outside the central nervous system.

Alzheimer’s Dementia

In patients with Alzheimer's Dementia participating in clinical trials, administration of single daily doses of 5 mg or 10 mg of donepezil hydrochloride produced steady-state inhibition of acetylcholinesterase activity (measured in erythrocyte membranes) of 63.6% and 77.3%, respectively when measured post dose. The inhibition of

acetylcholinesterase (AChE) in red blood cells by donepezil hydrochloride has been shown to correlate to changes in ADAS-cog, a sensitive scale that examines selected aspects of cognition. The potential for donepezil hydrochloride to alter the course of the underlying neuropathology has not been studied. Thus, donepezil can not be considered to have any effect on the progress of the disease.

Efficacy of treatment of Alzheimer's Dementia with Donesyn has been investigated in four placebo-controlled trials, 2 trials of 6-month duration and 2 trials of 1-year duration.

In the 6 months clinical trial, an analysis was done at the conclusion of donepezil treatment using a combination of three efficacy criteria: the ADAS-Cog (a measure of cognitive performance), the Clinician Interview Based Impression of Change with Caregiver Input (a measure of global function) and the Activities of Daily Living Subscale of the Clinical Dementia Rating Scale (a measure of capabilities in community affairs, home and hobbies and personal care).

Patients who fulfilled the criteria listed below were considered treatment responders.

Response = Improvement of ADAS-Cog of at least 4 points
No deterioration of CIBIC
No Deterioration of Activities of Daily Living Subscale of the Clinical Dementia Rating Scale

	% Response	
	Intent to treat	Evaluable
	Population n=365	Population n=352
Placebo Group	10%	10%
Donepezil hydrochloride 5-mg Group	18%	18%
Donepezil hydrochloride 10-mg Group	21%	22%

*p < 0.05
**p < 0.01

Donepezil hydrochloride produced a dose-dependent statistically significant increase in the percentage of patients who were judged treatment responders.

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 did not affect the absorption of donepezil hydrochloride.

Distribution: Donepezil hydrochloride is approximately 95% 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. However, in a mass balance study conducted in healthy male volunteers, 240 hours after the administration of a single 5 mg dose of 14C-labelled donepezil hydrochloride, approximately 28% of the label remained unrecovered. This suggests that donepezil hydrochloride and/or its metabolites may persist in the body for more than 10 days.

Metabolism/Excretion: Donepezil hydrochloride is both excreted in the urine intact and metabolised by the cytochrome P450 system to multiple metabolites, not all of which have been identified. Following administration of a single 5 mg dose of 14C-labelled donepezil hydrochloride, plasma radioactivity, expressed as a percent of the administered dose,

was present primarily as intact donepezil hydrochloride (30%), 6-O-desmethyldonepezil (11% – only metabolite that exhibits activity similar to donepezil hydrochloride), donepezil-cis-N-oxide (9%), 5-O-desmethyldonepezil (7%) and the glucuronide conjugate of 5-O-desmethyldonepezil (3%). 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. 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. 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.

Patients with mild to moderate hepatic impairment had increased donepezil steady state concentrations; mean AUC by 48% and mean Cmax by 39% (see section 4.2).

5.3 Preclinical safety data

Extensive testing in experimental animals has demonstrated that this compound causes few effects other than the intended pharmacological effects consistent with its action as a cholinergic stimulator (see section 4.9). Donepezil is not mutagenic in bacterial and mammalian cell mutation assays. Some clastogenic effects were observed *in vitro* at concentrations overtly toxic to the cells and more than 3000 times the steady-state plasma concentrations. No clastogenic or other genotoxic effects were observed in the mouse micronucleus model *in vivo*. There was no evidence of oncogenic potential in long-term carcinogenicity studies in either rats or mice.

Donepezil hydrochloride had no effect on fertility in rats, and was not teratogenic in rats or rabbits**,** but had a slight effect on still-births and early pup survival when administered to pregnant rats at 50 times the human dose (see section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polacrilin potassium
Cellulose, microcrystalline
Lactose monohydrate (spray dried)
Monosodium citrate anhydrous
Aspartame E951
Croscarmellose sodium
Silica colloidal anhydrous
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original blister in order to protect from moisture.

6.5 Nature and contents of container

PVC/ PCTFE/Aluminium and Aluminium/Aluminium blisters
Pack sizes:
10, 14, 28, 30, 56, 98, 126, 154 and 196 orodispersible tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 126/214/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th January 2012

10 DATE OF REVISION OF THE TEXT

April 2016