

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0915/020/001

Case No: 2045697

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Helsinn Birex Therapeutics Ltd

Damastown, Mulhuddart, Dublin 15, Ireland

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Donelinn 5mg film-coated tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **11/09/2009** until **10/09/2014**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Donelinn 5mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of donepezil hydrochloride hydrochloride respectively.
Excipients include: Lactose 97.35mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablet.

White, round, biconvex film-coated tablets, 7 mm in diameter and marked DZ 5 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Donelinn tablets are indicated for the symptomatic treatment of mild or moderate dementia in Alzheimer's disease.

4.2 Posology and method of administration

Adults/elderly

The initial dose is 5 mg once a day. Donelinn 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 assess the first clinical responses to the treatment and obtain steady-state concentration of donepezil hydrochloride. Following the one month clinical assessment of treatment at 5 mg/day, the dose of Donelinn can be increased to 10 mg once a day. The maximum recommended daily dose is 10 mg. Clinical studies with doses higher than 10 mg/day have not been conducted.

Treatment shall be initiated and supervised by a doctor experienced in diagnosing and treating dementia in Alzheimer's disease. Diagnoses shall be according to accepted guidelines (e.g. DSM IV, ICD 10). Donelinn treatment shall only be initiated if a relative or another caregiver is ready to monitor regularly the use of the medicinal product for the patient. Maintenance treatment can be continued as long as the patient benefits from it. Clinical benefits of Donelinn use shall therefore be reevaluated regularly. Discontinuation of treatment should be considered when benefits are no longer observed. Individual response to Donelinn can not be predicted.

Upon discontinuation of treatment the beneficial affects observed during Donelinn use are gradually reduced. There are no signs of a rebound effect following abrupt discontinuation of treatment.

Renal and hepatic impairment

A similar dose schedule can be followed for patients with renal impairment as excretion of donepezil is not affected by such impairment.

Mild to moderate hepatic impairment can possibly increase exposure (see section 5.2), doses should therefore be adjusted with respect to individual tolerance. No data is available for patients with severe liver failure.

Children

Donelinn is not recommended for use in children.

4.3 Contraindications

Donelinn is contraindicated in patients with known hypersensitivity to donepezil hydrochloride, piperidine derivatives, or to any of the excipients. Donelinn is contraindicated during pregnancy, please refer to section 4.6 of SmPC.

4.4 Special warnings and precautions for use

Use of Donelinn in patients with severe dementia in Alzheimer's disease, dementia caused by other diseases or memory loss (e.g. age related dementia) has not been studied.

Anaesthesia: Donelinn, as a cholinesterase inhibitor, is likely to exaggerate the muscle relaxing effects of succinylcholine-type products during anaesthesia.

Cardiovascular conditions: Pharmacological action of cholinesterase inhibitors may have vasotonic effects on heart rate (e.g. bradycardia). The possibilities of this effect may be particularly important to patients with sick-sinus syndrome or other supraventricular cardiac conduction conditions, i.e. sinoatrial block and atrioventricular block. Cases of syncope and seizures have been reported. When examining such patients, heart block and long sinus pauses should be considered.

Gastro-intestinal conditions: Patients at increased risk for developing peptic ulcers, e.g. those with a history of peptic ulcer or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs) should be monitored for symptoms thereof. However, the clinical studies with donepezil showed no increase, relative to placebo, in the incidence of either peptic ulcers or gastrointestinal bleeding.

Genito-urinary: Although not observed in clinical trials of donepezil cholinomimetics may cause urethral obstruction.

Neurological conditions: Seizures. Cholinomimetics are considered having the potential to cause general seizures. Seizures can however also be caused by Alzheimer's disease.

Cholinomimetics can possibly worsen or increase extra pyramidal 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.

Concomitant use of Donelinn and other acetylcholinesterase inhibitors or agents which induce or inhibit the cholinergic system should be avoided.

Severe hepatic impairment: No information is available with respect to patients with severe hepatic impairment.

Donelinn contains lactose monohydrate. 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 Alzheimer'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 hydrochloride 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 patients 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 its metabolites do not inhibit the metabolism of theophylline, warfarin, cimetidine or digoxin in humans. Concurrent use of digoxin or cimetidine does not affect the metabolism of donepezil hydrochloride. *In vitro* studies have demonstrated that cytochrome P450 isoenzyme 3A4 and to some extent 2D6, take part in the metabolism of donepezil. Interaction studies *in vitro* demonstrate that ketoconazole, a CYP3A4 inhibitor, and quinidine, a CYP2D6 inhibitor, inhibit donepezil metabolism.

They, like other CYP3A4 inhibitors such as itraconazole and erythromycine and CYP2D6 inhibitors such as fluoxetine can therefore inhibit donepezil metabolism. In a study in healthy volunteers ketoconazole increased the concentration of donepezil about 30%. Enzyme inducers, such as rifampicine, phenytoin, carbamazepin and alcohol, can reduce blood concentration of donepezil. Caution should be exercised during concurrent use of these medicinal products since the extent of the inhibition or induction is not known. Donepezil hydrochloride can affect the efficacy of anticholinergic products. Synergistic activity is also possible in case of concomitant treatment with products such as succinylcholine, other neuro-muscular blocking agents, cholinergic agonists or beta-blockers, which affect cardiac conductivity.

4.6 Pregnancy and lactation

Pregnancy

Studies conducted in pregnant rats at doses up to approximately 80 times the human dose, and in pregnant rabbits at doses up to approximately 50 times the human dose did not disclose any teratogenic effects. However, in a study in which pregnant rats were given approximately 50 times the human dose from day 17 of gestation through day 20 postpartum, there was a slight increase in stillbirths and a slight decrease in pup survival through day 4 postpartum. No such effects were observed at the next lower dose tested, approximately 15 times the human dose.

There is no clinical information available regarding the use of donepezil in pregnant women. Donepezil should therefore not be used during pregnancy.

Lactation

It is not known whether donepezil hydrochloride is excreted in human breast milk and no studies have been carried out in lactating women. Women using donepezil should therefore not breast feed.

4.7 Effects on ability to drive and use machines

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

Alzheimer's dementia may impair the patients ability to drive or impair their ability to operate machinery. Additionally donepezil may cause fatigue, dizziness and muscle spasms, particularly at the beginning of treatment or upon dose elevation. The ability of Alzheimer's patients using donepezil to continue driving and operating complicated machinery should be evaluated regularly by the doctor supervising the treatment.

4.8 Undesirable effects

The most common adverse effects are diarrhoea, muscle spasms, fatigue, nausea, vomiting and sleep disturbances.

Adverse effects reported more often than in isolated cases are listed below, according to system organ class and frequency. Frequency is defined as: common (>1/100, <1/10), uncommon (>1/1.000, <1/100), rare (>1/10.000, <1/1.000), very common (>1/10), very rare (<1/10.000) and not known (cannot be estimated from available data).

System organ class	Common	Uncommon	Rare
Infections and infestations	Cold		
Metabolism and nutrition disorders	Anorexia		
Psychiatric disorders	Hallucinations** Agitation** Aggression**		
Nervous system disorders	Syncope* Dizziness Sleep disturbances	Seizures*	Extrapyramidal symptoms
Vascular disorders		Bradycardia	Sinus and atrium block Atrioventricular block
Gastrointestinal disorders	Diarrhoea (v.common) Vomiting Nausea (v.common) Abdominal pain	Gastrointestinal bleeding Gastric and duodenal ulcers	
Hepatobiliary disorders			Hepatic impairment, including hepatitis***
Skin and subcutaneous tissue disorders	Rash Pruritus		
Musculoskeletal and connective tissue disorders	Muscle spasms		
Renal and urinary disorders	Incontinence		
General disorders and administration site conditions	Headache (v.common) Fatigue Pain		
Investigations		Minor increase in serum muscle creatinin kinase	
Injury, poisoning and procedural complications	Accident		

* When examining patients who have suffered from seizures or syncope, heart block and sinus pauses should be considered (see section 4.4).

**Hallucinations have resolved upon dose reduction or discontinuation of treatment.

***In case of hepatic impairment from an unknown source, it should be considered to stop using Donelinn.

4.9 Overdose

The estimated mean 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.

Overdose with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, shock and convulsions. Increased muscle weakness is possible and may result in death if respiratory muscles are involved.

As in every case of overdose, general supportive measures should be applied. Tertiary anticholinergics such as atropine may be used as an antidote for Donelinn overdose. 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-administrated 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

Pharmacotherapeutic group: anti-dementia drugs; anticholinesterase; ATC-Code N06DA02

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

Alzheimers 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 of 63.3% and 77.3% respectively when measured post dose (measured in erythrocyte membranes). Correlation has been demonstrated between acetylcholine esterase (AChE) inhibition of donepezil hydrochloride in red blood cells and changes in ADAS-cog, a scale which examines cognitive function. The ability of donepezil hydrochloride to affect the underlying neuropathological development has not been studied. It can therefore not be assumed that Donelinn can affect the progression of the disease.

The results of donepezil hydrochloride treatment were studied in four placebo controlled studies, 2 lasted 6 months and 2 lasted 1 year.

In the 6 months clinical trial an appraisal was performed at the end of the donepezil treatment period using three standards for evaluation of efficacy: ADAS-Cog (to measure cognitive ability), Clinical Interview Based Impression of Changes with Caregiver Input, with respect to possible changes with the assistance of a close relative or caregiver (measures general ability) and then a scale for clinical cognitive deterioration with respect to daily activities (evaluates ability to participate in social interactions, at home, in recreation and with respect to own caretaking).

The patients who met the following criteria, were considered having responded to treatment:

Response = ADAS-Cog improved by at least 4 points.
No CIBIC reduction (Clinical Interview Based Impression of Changes).
No deterioration of daily activities based on measurements of clinical cognitive ability.

	% response	
	Group intended to treat n=365	Group successfully evaluated 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 demonstrates a dose related statistically significant increase in the ratio of patients considered responding to treatment.

5.2 Pharmacokinetic properties

General properties:

Absorption

Peak plasma concentration is reached about 3-4 hours after oral administration. Plasma concentration and area under the curve (AUC) increase in proportion with the dose. Terminal disposition half-life is about 70 hours and following repeated single daily dosing steady state is achieved gradually. Steady state is almost reached within 3 weeks following treatment initiation. Once steady state is achieved, only minor alterations in donepezil hydrochloride plasma levels and corresponding pharmacodynamic activity are observed over the course of the day.

Food intake does not affect the absorption of donepezil hydrochloride.

Distribution

Donepezil hydrochloride is approximately 95% bound to human plasma proteins. The binding of the active metabolite 6-O-desmethyl donepezil to plasma proteins is not known. The distribution of donepezil hydrochloride in various body tissues has not been definitively studied.

However in a study conducted in healthy male volunteers, approximately 28% of the administered dose remained unaccounted for, 240 hours after the administration of a single 5 mg dose of ^{14}C labelled donepezil hydrochloride. This indicates that donepezil hydrochloride and/or its metabolites are present in the body for more than 10 days.

Metabolism/excretion

Donepezil hydrochloride is both excreted in the urine intact and metabolised by the cytochrome P 450 system to multiple metabolites, not all of which have been identified. Following administration of a single 5 mg dose of ^{14}C labelled donepezil hydrochloride, plasma radioactivity, expressed as a percent of the administered dose, was measured primarily as intact donepezil hydrochloride (30%), 6-O-desmethyl donepezil (11% - the only metabolite that exhibits activity similar to donepezil hydrochloride), donepezil-cis-N-oxide (9%), 5-O-desmethyl donepezil (7%) and the glucuronide conjugate of 5-O-desmethyl donepezil (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 metabolism and urinary excretion as the primary routes of elimination.

There is no evidence suggesting entero-hepatic recirculation of donepezil hydrochloride and/or any of its metabolites.

Plasma half-life of donepezil is about 70 hours.

Sex, race and smoking history have not clinically significant effects on plasma levels of donepezil hydrochloride. No pharmacokinetic studies have been performed in healthy elderly individuals or those with Alzheimer's disease. Mean plasma levels are however almost the same as in healthy young volunteers.

Steady state concentration increased in patients with mild to moderate hepatic impairment, AUC 48% on the average and C_{\max} 39% on the average (see section 4.2).

5.3 Preclinical safety data

Extensive testing in 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 was neither mutagenic in bacterial nor animal cells. Some clastogenic effects were observed *in vitro* but only at levels approaching those obviously toxic in cells and more than 3,000 times the steady state plasma levels. No clastogenic effects or signs of other genotoxic effects were observed in the mouse micronucleus model *in vivo*. Long term carcinogenic studies did not demonstrate any oncogenic effects neither in rats nor mice.

Donepezil hydrochloride did not affect fertility in rats and no teratogenic effects were observed in rats and rabbits. A minor increase in still births was however observed and life expectancy of pups slightly reduced, when the medicinal product was been administered to pregnant rats at 50 times the recommended doses for humans (see section 4.6 above).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Maize starch
Magnesium stearate
Polyvinyl alcohol
Titanium dioxide (E 171)
Macrogol 3350
Talc

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 storage conditions.

6.5 Nature and contents of container

PVC/aluminium blister foil
HDPE bottle with LDPE cap

Pack sizes:
Foil: 7, 14, 28, 30, 50, 56, 60, 98, 100, 250 tablets.
HDPE bottle: 28, 30, 100, 250 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Helsinn Birex Thereapeutics Ltd.
Damastown
Mulhuddart
Dublin 15
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 915/20/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th September 2009

10 DATE OF REVISION OF THE TEXT