

IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA1063/036/001

Case No: 2059594

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

Niche Generics Limited

1, The Cam Centre, Wilbury Way, Hitchin, Hertfordshire SG4 OTW, United Kingdom

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

Arizime 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 **28/05/2010** until **27/05/2015**.

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

Arizime 5mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5mg donepezil hydrochloride (as the monohydrate), equivalent to 4.56mg of donepezil.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet

White or almost white, round, biconvex film-coated tablets embossed with stylized E 381 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Arizime is indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia.

4.2 Posology and method of administration

Adults/Elderly

Treatment is initiated at 5 mg once a day. It 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 to be achieved. Following a one-month clinical assessment of treatment at 5 mg/day, the dose of Arizime can be increased to 10 mg once a day. 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 Arizime is seen. No rebound effect has been detected after an abrupt discontinuation of its administration.

Renal and hepatic impairment

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

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

Arizime is not recommended for use in children.

4.3 Contraindications

Arizime is contraindicated in patients with hypersensitivity to donepezil hydrochloride, piperidine derivatives, or to any of the excipients.

4.4 Special warnings and precautions for use

The efficacy 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 yet been established.

Anaesthesia

Arizime 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 sinus 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 non-steroidal 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

Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity may also be a manifestation of Alzheimer's disease.

Cholinomimetics may have a 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 donepezil hydrochloride 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.

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 %) 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 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 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 neuromuscular blocking agents or cholinergic agonists or beta blocking agents which have effects on cardiac conduction.

4.6 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 postnatal toxicity (see section 5.3). The potential risk for humans is unknown.

Arizime should not be used during pregnancy unless clearly necessary.

Lactation

Donepezil is excreted in the milk of rats. It is not known whether donepezil 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

Donepezil 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 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. Dizziness, headaches, pain, accidents and the common cold have also been reported. In most cases these go away without having to stop treatment.

Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency.

Frequencies are defined as: very common (≥1/10), common (≥1/100,<1/10), uncommon (≥1/1,000,<1/100), rare (≥1/10,000,<1/1,000), very rare (<1/10, 000) and not known (cannot be estimated from available data).

System organ class	Very common	Common	Uncommon	Rare
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
Cardiac disorders			Bradycardia	Sino-atrial block Atrioventricular block
Gastrointestinal disorders	Diarrhoea Nausea	Vomiting Abdominal disturbance	Gastrointestinal haemorrhage Gastric and duodenal ulcers	
Hepatobiliary disorders				Liver dysfunction including hepatitis***
Skin and subcutaneous tissue disorders		Rash Pruritus		
Musculoskeletal and connective tissue disorders		Muscle cramps		
Renal and urinary disorders		Urinary incontinence		
General disorders and administration site conditions	Headache	Fatigue Pain		
Investigations			Minor increase in serum concentration of muscle creatine kinase	
Injury, poisoning and procedural complications		Accident		

* In investigating patients for syncope or seizure the possibility of heart block or long sinus 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 Arizime should be considered

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.

Overdose 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 Arizime overdosage. Intravenous atropine sulphate titrated to effect is recommended: an initial dose of 1 mg to 2 mg iv. with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when coadministered with quaternary anticholinergics such as glycopyrrolate. It is not known whether donepezil hydrochloride and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration).

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 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.

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 which examines selected aspects of cognition. The potential for donepezil hydrochloride to alter the course of the underlying neuropathology has not been studied. Thus donepezil hydrochloride cannot be considered to have any effect on the progress of the disease.

Efficacy of treatment with donepezil 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, and no deterioration of CIBIC, and no deterioration of Activities of Daily Living Subscale of the Clinical Dementia Rating Scale.

	% Response	
	Intent to treat population n=365	Evaluable population n=352
Placebo group	10 %	10 %
Donepezil HCl 5 mg-Group	18 % *	18 % *
Donepezil HCl 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. 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. 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-desmethyl donepezil (11 %- 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 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 dementia patients 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 C_{max} 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

Core:

Microcrystalline cellulose

Hydroxypropylcellulose

Magnesium stearate

Film-coating:

Opadry Y-1-7000 White: hypromellose, titanium dioxide (E 171) and macrogol 400.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

28 or 56 film-coated tablets are supplied in OPA/Al/PVC//Alu foil or in PVC/PVdC//Alu foil blister in carton box. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Niche Generics Limited

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Hitchin

Hertfordshire SG4 OTW

United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1063/36/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th May 2010

10 DATE OF REVISION OF THE TEXT