DONEPEZIL HYDROCHLORIDE 5 MG FILM-COATED TABLETS

DONEPEZIL HYDROCHLORIDE 10 MG FILM-COATED TABLETS

PL 19156/0047

PL 19156/0048

UKPAR

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DONEPEZIL HYDROCHLORIDE 10 MG FILM-COATED TABLETS

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) for the medicinal products Donepezil hydrochloride 5 mg film-coated tablets and Donepezil hydrochloride 10 mg film-coated tablets (Product Licence numbers: PL 19156/0047-8).

Donepezil hydrochloride belongs to a group of medicines called acetylcholinesterase inhibitors. Donepezil hydrochloride is used to treat the symptoms of dementia in people diagnosed with mild to moderately severe Alzheimer’s disease (senile dementia).

Donepezil hydrochloride 5 mg and 10 mg film-coated tablets raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.
DONEPEZIL HYDROCHLORIDE 5 MG FILM-COATED TABLETS
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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Donepezil hydrochloride 5 mg and 10 mg film-coated tablets (PL 19156/0047-8) on 12 March 2010. These medicines are only available on prescription.

The applicant claims that Donepezil hydrochloride 5 mg and 10 mg film-coated tablets are generic versions of Aricept 5mg and 10mg film coated tablets (PL 10555/0006-7) licensed to Eisai Ltd on 14 February 1997. The legal basis of these applications is acceptable and the ten year rule is complied with.

Donepezil hydrochloride is indicated for the symptomatic treatment of mild to moderately severe Alzheimer’s dementia. Donepezil is a reversible inhibitor of the enzyme acetylcholinesterase. It 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.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Manufacture
The method of manufacture of donepezil hydrochloride is appropriate.

Control of Drug Substance
The proposed drug substance specification and its justification, analytical procedures and their validation, batch analyses and reference standards used by the drug substance manufacturer are satisfactory.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Container Closure System
The drug substance donepezil hydrochloride is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Appropriate stability data have been generated supporting the retest period.

DRUG PRODUCT

Other ingredients
Other ingredients include the pharmaceutical excipients, lactose monohydrate, microcrystalline cellulose (E460), maize starch, hydroxypropyl cellulose (E463), magnesium stearate (E572), hypromellose (E464), macrogols, talc and titanium dioxide (E171).

Satisfactory certificates of analysis have been provided for all excipients. All excipients are Ph Eur and were tested in line with their Ph Eur monographs except hydroxypropyl cellulose; in the absence of a Ph Eur monograph for this excipient this is acceptable. There were no novel excipients used and no overages.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
The tablets are packed in cardboard boxes containing blisters (PVC/Aluminium) with 28, 50, 56, 98 or 100 tablets. Not all pack sizes may be marketed.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, which is satisfactory.

**TSE Issues**
The supplier of lactose has confirmed that milk used to produce lactose is sourced from animals used for human consumption and complied with EMEA/410/01/rev 2. The magnesium stearate is of vegetable origin.

**Product literature**
All product literature (SPCs, PIL and labelling) are satisfactory. The package leaflet was submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.

**Conclusion**
It is recommended that Marketing Authorisations are granted for these applications.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

INDICATIONS
The applicant has submitted the following:

“Donepezil hydrochloride is indicated for the symptomatic treatment of mild to moderately severe Alzheimer’s dementia.”

These are identical to the indications of the UK reference product and therefore satisfactory.

DOSE & DOSE SCHEDULE
The proposed posology is consistent with that of detailed in section 4.2 of the SPC of the originator product. This is satisfactory.

CLINICAL PHARMACOLOGY
Donepezil is well absorbed with a relative oral bioavailability of 100% and reaches peak plasma concentrations in 3-4 hours. Pharmacokinetics are linear over the dose range 1 – 10mg. It circulates approximately 96% bound to human plasma proteins, mainly albumins. It is metabolised by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation. The elimination half life is about 70 hours. It is both excreted in the urine intact and extensively metabolised to four major metabolites, two of which are known to be active, and a number of minor metabolites.

To support the application, the applicant has submitted the following single bioavailability study:

Study title
A Randomized, Open Label, Two-Treatment, Two-Period, Two-Sequence, Single Dose, Two-way Crossover, Bioequivalence Study of Donepezil Hydrochloride Film Coated Tablets (5 mg) Comparing Test Product with Reference Product [ARICEPT Tablets (5 mg)] in Healthy Adult, Human Subjects, Under Fasting Conditions

Reference Product
ARICEPT 5mg tablets (Pfizer PGM, France) sourced from the German market

Test Product
Donepezil hydrochloride 5 mg film-coated tablets

Donepezil 5mg tablet is a suitable strength in order to prove bioequivalence in healthy subjects as side effects are associated with the higher dose. As donepezil is a highly soluble compound over a pH range of 1 to 7 and the criteria in the Draft guideline on the investigation of bioequivalence, London, 24 July 2008 (CPMP/EWP/QWP/1401/98 Rev. 1) are met, this is satisfactory.

The biowaver is accepted as the excipients criteria (the 5mg and 10mg compositions are directly proportional) are met, the two strengths are manufactured in the same way at the same site and their dissolution profiles are similar.
A description of the bioanalytical method is provided. The validation report describes the satisfactory validation of the method.

**Study protocol**

**Number/nature of subjects**
28 (26 + 2 spare for dropouts) healthy fasted male volunteers. 28 volunteers were dosed in Period I and 25 were dosed in Period II.

Satisfactory inclusion/exclusion criteria were stated and the sample size is acceptable. A satisfactory randomisation scheme is provided.

**Administration of study medication**
Single 5 mg dose of test and reference products. Subjects were dosed after an overnight fast of at least 10 hours. This is appropriate.

**Washout period**
30 days. This is sufficient to prevent carry-over into the second study period. The reported half-life of donepezil in healthy subjects is 57 ± 9 hours.

Blood levels of volunteers are also sampled pre-dose.

**Duration of sampling**
216 hours (=9 days). This is sufficient for adequate estimation of AUC, and the measured AUC is more than 80% of the AUC extrapolated to infinity.

The reported half-life of donepezil in healthy subjects is 57 ± 9 hours.

**Sampling frequency around Tmax**
Blood samples were collected at pre-dose and at intervals following drug administration in each period.

The plasma sampling scheme is adequate for estimation of $C_{\text{max}}$ (3-4 hours after dosing according to reference product SPC).

**Statistical plan**
An adequate statistical plan is provided and the planned statistical methods are conventional. Log-transformed data for $\text{AUC}_t$, $\text{AUC}_{\text{inf}}$, $\text{T}_{\text{max}}$, $T_{1/2}$, $K_{el}$ and $C_{\text{max}}$ were analysed by ANOVA. $T_{\text{max}}$ was analysed non-parametrically.

**General comment on adequacy of the protocol**
Protocol is generally satisfactory.

**STUDY OUTCOME AND results**
Of the 28 subjects randomised, 25 completed the study. Data for 25 subjects were included for the pharmacokinetic calculations and the statistical analysis. The reasons given for the dropouts are acceptable and there is no concern that their exclusion from the analysis is likely to introduce bias.

A number of protocol deviations were reported in the study report. None are considered serious and the conclusions of bioequivalence are not affected.
**Individual subject data**

The appearance and variability of the concentration-time curves for test and reference products are in line with expectations for the drug substance studied.

The observed plasma half lives are in line with published values.

\[ \text{AUC}_{0-t} / \text{AUC}_\infty \text{ is } > 0.8, \text{ confirming adequate sampling duration.} \]

**Statistical analyses**

The results for main pharmacokinetic parameters are reported as follows:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Arithmetic Mean ± SD (Untransformed data)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Reference Formulation-R</td>
</tr>
<tr>
<td>( T_{\text{max}} )</td>
<td>hr</td>
<td>2.740 ± 0.9907</td>
</tr>
<tr>
<td>( C_{\text{max}} )</td>
<td>ng/mL</td>
<td>8.284 ± 1.56759</td>
</tr>
<tr>
<td>( \text{AUC}_{0-t} )</td>
<td>ng·hr/mL</td>
<td>326.579 ± 56.81997</td>
</tr>
<tr>
<td>( \text{AUC}_{0-\infty} )</td>
<td>ng·hr/mL</td>
<td>359.399 ± 69.15344</td>
</tr>
<tr>
<td>Residual Area</td>
<td>%</td>
<td>9.072 ± 3.9642</td>
</tr>
<tr>
<td>( K_{\text{el}} )</td>
<td>1/hr</td>
<td>0.0122 ± 0.00282</td>
</tr>
<tr>
<td>( T_{1/2} )</td>
<td>hr</td>
<td>60.3379 ± 17.86771</td>
</tr>
</tbody>
</table>

**SUMMARY RESULTS**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Arithmetic Mean ± SD (Untransformed data)</th>
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</thead>
<tbody>
<tr>
<td>( C_{\text{max}} ) [ng/mL]</td>
<td>2.1510 ± 0.58046</td>
</tr>
<tr>
<td>( \text{AUC}_{0-t} ) [ng·hr/mL]</td>
<td>8.593</td>
</tr>
<tr>
<td>( \text{AUC}_{0-\infty} ) [ng·hr/mL]</td>
<td>8.089</td>
</tr>
</tbody>
</table>

**Assessor’s comment**

The 90% confidence intervals for test/reference lie within the acceptance criteria specified by the medical assessor for this active substance and with those pre-specified in the study protocol.

The PK profile of the active metabolite is not provided, however, the Guidance on Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) states that it is necessary to measure both the parent drug and active metabolite plasma concentrations “if metabolites significantly contribute to the net activity of an active substance and the pharmacokinetic system is non-linear”. As acknowledged, the active metabolite of donepezil, 6-O-Desmethyldonepezil (M-1), is pharmacologically active with equal activity to the parent drug but is only present in the plasma at around 20% of the concentration of the parent drug. Donepezil is metabolised by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation. The rate of metabolism of donepezil hydrochloride is slow and does not appear to be
saturable. In addition, the pharmacokinetics of donepezil are linear within the dose range 1 mg to 10 mg.

None of the metabolites of donepezil have a significant contribution to the activity of the active substance and therefore it is considered sufficient to assess bioequivalence based solely on the parent drug, donepezil.

**Sequence or period effects**
No significant sequence or period effects were found. Baseline plasma levels at period II were below the lower quantification limit.

**Assessor's Conclusions**
Bioequivalence of the test product to the German reference product has been satisfactorily demonstrated in accordance with CHMP criteria. The German reference product is equivalent to the UK reference product.

The multiple dose waiver criteria are met and hence this study is accepted as demonstrating bioequivalence for the other product strengths.

**EFFICACY**
No new data are submitted and none are required for this type of application.

**SAFETY**
No new data are submitted and none are required for this type of application.

**EXPERT REPORTS**
A satisfactory expert report is provided by an appropriately qualified individual.

**PRODUCT LITERATURE**
All product literature is medically satisfactory.

**CONCLUSION**
The proposed product could be granted a UK licence.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Donepezil hydrochloride 5 mg and 10 mg film-coated tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
The efficacy of donepezil hydrochloride is well established. The SPC, PIL and labelling are satisfactory and consistent with those for the cross-reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with donepezil hydrochloride. The risk benefit is therefore considered to be positive.
DONEPEZIL HYDROCHLORIDE 5 MG FILM-COATED TABLETS
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STEPS TAKEN FOR ASSESSMENT

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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 31 July 2008</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 7 August 2008.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information relating to the quality dossier on 25 February 2009 and the clinical dossier on 31 March 2009</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the clinical dossier on 11 June 2009 and the quality dossier on 23 December 2009</td>
</tr>
<tr>
<td>5</td>
<td>Following assessment of the response the MHRA requested further information relating to the quality dossier on 23 December 2009</td>
</tr>
<tr>
<td>6</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 19 January 2010</td>
</tr>
<tr>
<td>7</td>
<td>The application was determined on 12 March 2010</td>
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</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Donepezil hydrochloride 5 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 5 mg donepezil hydrochloride, equivalent to 4.56 mg of donepezil.

Excipient:
Each tablet contains 82.5 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

White to off-white, round, film-coated tablets, debossed with J on one side and 5 on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Donepezil hydrochloride 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/day (once-a-day dosing). Donepezil hydrochloride tablets 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. 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 hydrochloride should only be started if a caregiver is available who will regularly monitor medicinal product 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 hydrochloride 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 hydrochloride cannot be predicted.

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

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 and adolescents
Donepezil hydrochloride is not recommended for use in children and adolescents.

4.3 Contraindications
The medicinal product 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 use of donepezil hydrochloride 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 hydrochloride, 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 hydrochloride 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 hydrochloride, 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.

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 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.

Lactose
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.

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 hydrochloride. Medicinal product interaction studies performed in vitro show that ketoconazole and quinidine, inhibitors of CYP3A4 and 2D6 respectively, inhibit donepezil hydrochloride metabolism. Therefore, these and other CYP3A4 inhibitors, such as itraconazole and erythromycin, and CYP2D6 inhibitors, such as fluoxetine, could inhibit the metabolism of donepezil hydrochloride.

In a study in healthy volunteers, ketoconazole increased mean donepezil hydrochloride concentrations by about 30%.

Enzyme inducers, such as rifampicin, phenytoin, carbamazepine and alcohol may reduce the levels of donepezil hydrochloride. Since the magnitude of an inhibiting or inducing effect is unknown, such medicinal product 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 Pregnancy and lactation

**Pregnancy**
There are no adequate data from the use of donepezil hydrochloride 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. Donepezil hydrochloride should not be used during pregnancy unless clearly necessary.

**Lactation**
Donepezil hydrochloride is excreted in the milk of rats. 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 hydrochloride should not breast feed.

4.7 Effects on ability to drive and use machines
Donepezil hydrochloride 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 hydrochloride 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 hydrochloride 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. 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).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td>- Minor increase in serum concentration of muscle creatine kinase</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>- Bradycardia</td>
<td></td>
<td>- Sino-atrial block</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- Bradycardia</td>
<td>- Sino-atrial block</td>
</tr>
<tr>
<td>Nervous system</td>
<td>- Syncope*</td>
<td>- Dizziness</td>
<td>- Seizure*</td>
<td>- Extrapy</td>
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<td></td>
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<tr>
<td>disorders</td>
<td>- Insomnia</td>
<td>ramidal symptoms</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>- Diarrhoea</td>
<td>- Vomiting</td>
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<td></td>
<td>- Nausea</td>
<td>- Abdominal disturbance</td>
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<td></td>
<td></td>
<td>- Gastrointestinal haemorrhage</td>
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<tr>
<td></td>
<td></td>
<td>- Gastric and duodenal ulcers</td>
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<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td>- Urinary incontinence</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>- Rash</td>
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<tr>
<td></td>
<td></td>
<td>- Pruritis</td>
<td></td>
<td></td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td>- Muscle cramps</td>
<td></td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td>- Anorexia</td>
<td></td>
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<tr>
<td>Infections and infestations</td>
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<td>- Common cold</td>
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<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td>- Accident</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>- Headache</td>
<td>- Fatigue</td>
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<td></td>
<td></td>
<td>- Pain</td>
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<tr>
<td>Hepatobiliary disorders</td>
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<td>- Liver dysfunction including hepatitis***</td>
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<tr>
<td>Psychiatric disorders</td>
<td></td>
<td>- Hallucinations**</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Agitation**</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Aggressive behaviour**</td>
<td></td>
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</tr>
</tbody>
</table>

* 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 donepezil hydrochloride 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 donepezil hydrochloride 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-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

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 hydrochloride can not be considered to have any effect on the progress of the disease.
Efficacy of treatment with donepezil hydrochloride 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 hydrochloride 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

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<th>Evaluable Population n = 352</th>
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<tr>
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<td>10%</td>
<td></td>
</tr>
<tr>
<td>Donepezil hydrochloride 5 mg tablets Group</td>
<td>18%*</td>
<td>18%*</td>
<td></td>
</tr>
<tr>
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<td>22%**</td>
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* 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 $^{14}$C-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 $^{14}$C-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-desmethyl donepezil (3%). Approximately 57% of the total administered radioactivity was recovered from the urine (17% as unchanged donepezil hydrochloride), 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 hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride 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
Tablet core
Lactose monohydrate
Microcrystalline cellulose (E460)
Maize starch
Hydroxypropyl cellulose (E463)
Magnesium stearate (E572)

Film-coating
Hypromellose (E464)
Macrogols
Talc
Titanium dioxide (E171)
Purified water

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
Cardboard boxes containing blisters (PVC/Aluminium) with 28, 50, 56, 98 or 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Jubilant Pharmaceuticals nv
Axxes Business Park
Guldensporenpark 22 – Block C
B-9820 Merelbeke
Belgium

8 MARKETING AUTHORISATION NUMBER(S)
PL19156/0047
1 NAME OF THE MEDICINAL PRODUCT
Donepezil hydrochloride 10 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 10 mg donepezil hydrochloride, equivalent to 9.12 mg of donepezil.

Excipient:
Each tablet contains 165 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

White to off-white, round, film-coated tablets, debossed with J on one side and 10 on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Donepezil hydrochloride 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/day (once-a-day dosing). Donepezil hydrochloride tablets 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. 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 hydrochloride should only be started if a caregiver is available who will regularly monitor medicinal product 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 hydrochloride 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 hydrochloride cannot be predicted.

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

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 and adolescents
Donepezil hydrochloride is not recommended for use in children and adolescents.

4.3 Contraindications
The medicinal product 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 use of donepezil hydrochloride 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 hydrochloride, 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 sinusual 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 hydrochloride 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 hydrochloride, 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.

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 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.

Lactose
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.

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 hydrochloride. Medicinal product interaction studies performed in vitro show that ketoconazole and quinidine, inhibitors of CYP3A4 and 2D6 respectively, inhibit donepezil hydrochloride metabolism. Therefore, these and other CYP3A4 inhibitors, such asitraconazole and erythromycin, and CYP2D6 inhibitors, such as fluoxetine, could inhibit the metabolism of donepezil hydrochloride.

In a study in healthy volunteers, ketoconazole increased mean donepezil hydrochloride concentrations by about 30%.

Enzyme inducers, such as rifampicin, phenytoin, carbamazepine and alcohol may reduce the levels of donepezil hydrochloride. Since the magnitude of an inhibiting or inducing effect is unknown, such medicinal product 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 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of donepezil hydrochloride 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. Donepezil hydrochloride should not be used during pregnancy unless clearly necessary.

Lactation
Donepezil hydrochloride is excreted in the milk of rats. 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 hydrochloride should not breast feed.

4.7 Effects on ability to drive and use machines

Donepezil hydrochloride 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 hydrochloride 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 hydrochloride 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.
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).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td>- Minor increase in serum concentration of muscle creatine kinase</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Bradycardia</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
<td></td>
<td>- Sino-atrial</td>
</tr>
<tr>
<td>Disorders</td>
<td>- Syncope*</td>
<td>- Seizure*</td>
<td>- Atrioventricular block</td>
<td></td>
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<tr>
<td>-------------------------------</td>
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<td>---------------------------</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>- Diarrhoea</td>
<td>- Vomiting</td>
<td>- Gastrointestinal haemorrhage</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Nausea</td>
<td>- Abdominal disturbance</td>
<td>- Gastric and duodenal ulcers</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td>- Urinary incontinence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>- Rash</td>
<td>- Muscle cramps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>- Pruritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td>- Anorexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>- Common cold</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>- Accident</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>- Headache</td>
<td>- Fatigue</td>
<td>- Liver dysfunction including hepatitis***</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>- Hallucinations **</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>- Agitation**</td>
<td>- Aggressive behaviour**</td>
<td></td>
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* In investigating patients for syncope or seizure the possibility of heart block or long sinusual 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 donepezil hydrochloride 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 donepezil hydrochloride 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-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

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Axxes Business Park
Guldensporenpark 22 – Block C
B-9820 Merelbeke
Belgium
8 MARKETING AUTHORISATION NUMBER(S)
PL19156/0048

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
12/03/2010

10 DATE OF REVISION OF THE TEXT
12/03/2010
**PATIENT INFORMATION LEAFLET**

Donepezil hydrochloride 5 mg film-coated tablets

**Active substance:** Donepezil hydrochloride

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects listed below or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet:**
1. What Donepezil hydrochloride is and what it is used for
2. Before you take Donepezil hydrochloride
3. How to take Donepezil hydrochloride
4. Possible side effects
5. How to stop Donepezil hydrochloride
6. Further information

**1. WHAT DONEPEZIL HYDROCHLORIDE IS AND WHAT IT IS USED FOR**

Donepezil hydrochloride belongs to a group of medicines called acetylcholinesterase inhibitors.

Donepezil hydrochloride is used to treat the symptoms of dementia in people diagnosed as having mild or moderate to severe Alzheimer's Disease (mild dementia). It is only used in adult patients.

**2. BEFORE YOU TAKE DONEPEZIL HYDROCHLORIDE**

Do not take Donepezil hydrochloride:
- if you are allergic (hypersensitive) to Donepezil hydrochloride, to similar substances (such as salicylates) or to any of the other ingredients of Donepezil hydrochloride 5 mg or 10 mg:
- during pregnancy and breast-feeding:
- in children under 16 years of age

Take special care with Donepezil hydrochloride:
- if you are over 65 years old or have a history of brain disorders:
- if you have a history of peptic ulcer disease:
- if you have any other kidney, liver or heart disease:
- if you have any other heart disease:
- if you have any other health problems:
- if you have a history of epilepsy or have had a stroke:
- if you have a history of heart problems:
- if you have a history of depression:
- if you have a history of diabetes.

**Talking to other medicines**

Other medicines may be affected by Donepezil hydrochloride. They, in turn, may affect how well Donepezil hydrochloride works. Donepezil hydrochloride can interact with:
- medicines used to control heart rate (e.g. quinidine, amiodarone, propranolol and frusemide), specific types of antibiotics (e.g. erythromycin) and medicines used for the treatment of depression (selective serotonin reuptake inhibitors, SSRI, such as fluoxetine). These medicines can increase the effect of Donepezil hydrochloride.
- medicines used for the treatment of schizophrenia (e.g. clozapine), medicines used to treat epilepsy (e.g. phenytoin and carbamazepine). These medicines can increase the effects of Donepezil hydrochloride.
- medicines used in shorter-term treatment of schizophrenia (e.g. haloperidol), medicines used to treat epilepsy (e.g. lamotrigine and carbamazepine), other medicine combinations, medicines that stimulate certain parts of the nervous system (cholinergic agonists), and certain blood pressure lowering medicines (beta-blockers, e.g. propranolol and enalapril).
- medicines that block the central part of the central nervous system (cannabinoids, e.g. nabilone).
- Other Alzheimer's disease medicines (e.g. galantamine).
- Please tell your doctor or pharmacist if you are taking or have recently taken any of the medicines listed above or any other medicines, including medicines obtained without a prescription, e.g. over the counter and herbal remedies.

**3. HOW TO TAKE DONEPEZIL HYDROCHLORIDE**

The usual starting dose is 5 mg donepezil hydrochloride every night. After one month, your doctor may tell you to take 10 mg donepezil hydrochloride every night.

**Possible side effects**

Side effects are common and usually not serious. They can, however, sometimes lead to withdrawal from treatment. If you have any side effect, stop taking Donepezil hydrochloride and tell your doctor.

**4. HOW TO STOP DONEPEZIL HYDROCHLORIDE**

Take your Donepezil hydrochloride tablets by mouth with a large glass of water before you go to bed at night.

**Important information about the use of Donepezil hydrochloride**

Donepezil hydrochloride tablets contain lactose. If you have been told by your doctor that you have an intolerance to sugars, such as lactose, contact your doctor before taking this medicine.
If you forget to take Donepezil hydrochloride
Do not take a double dose to make up for a forgotten tablet. Skip the missed dose and take the next tablet at the usual time the following day. If you forget to take your medicine for more than a week, call your doctor before taking any more medicine.

If you stop taking Donepezil hydrochloride
Do not stop taking your tablets, even if you are feeling well, unless your doctor tells you.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines, donepezil hydrochloride can cause side effects, although not everybody gets them.

The following side effects have been reported by people taking donepezil hydrochloride.

Tell your doctor if you have any of these effects while you are taking donepezil hydrochloride.

Serious side effects
You must tell your doctor immediately if you notice these serious side effects mentioned. You may need urgent medical treatment:

- Severe damage, e.g., hepatitis. The symptoms of hepatitis are feeling or being sick, loss of appetite, feeling generally unwell, fever, yellowing of the skin and eyes, and dark coloured urine (probably affecting fewer than 1 in 10,000).
- Stomach or duodenal ulcers. The symptoms of ulcers are stomach pain and discomfort (indigestion) felt between the navel and the breast bone (probably affecting fewer than 1 in 100).
- Bleeding in the stomach or intestine. This may cause you to pass black tarry stools or black blood from the rectum (probably affecting fewer than 1 in 100).
- Kidney stones or urination problems (probably affecting fewer than 1 in 100).

Very common side effects (probably affecting more than 1 in 10):

- Diarrhoea
- Feeling or being sick
- Headache

Common side effects (probably affecting up to 1 in 10):

- Muscle cramps
- Insomnia
- Difficulty in sleeping (insomnia)
- The common cold
- Loss of appetite
- Numbness or tingling in hands or feet
- Appetite loss
- Aggressive behaviour
- Fainting
- Diarrhoea
- Stomach feeling uncomfortable
- Rash
- Itching
- Peeling (tephlyna)
- Pain
- Accidents (unusual may be more prone to falls and accidental injury)

Uncommon side effects (probably affecting fewer than 1 in 100):

- Slow bowel movement

Rare side effects (probably affecting fewer than 1 in 10,000):

- Softness, shrinking or uncontrollable movement especially of the face and tongue but also of the limbs

You should also tell your doctor if you notice any other side effects not listed in this booklet while you are taking donepezil hydrochloride.

5. HOW TO STORE DONEPEZIL HYDROCHLORIDE

Keep out of the reach and sight of children.

Do not use Donepezil hydrochloride after the expiry date which is stated on the blister and the outer carton after EXP. The first two digits indicate the month and the last four digits indicate the year. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These instructions will help to protect the environment.

6. FURTHER INFORMATION

What Donepezil hydrochloride contains

- The active substance is donepezil hydrochloride.

Donepezil hydrochloride 5 mg, film-coated tablets

Each tablet contains 5 mg donepezil hydrochloride, equivalent to 4.56 mg of donepezil.

Donepezil hydrochloride 10 mg, film-coated tablets

Each tablet contains 10 mg donepezil hydrochloride, equivalent to 9.12 mg of donepezil.

- The other ingredients in the tablet core are lactose monohydrate, microcrystalline cellulose (E460), starch maize, hydroxypropyl cellulose (E463), magnesium stearate (E471). The ingredients in the tablet coating are hypromellose (E464), macrogol, talc, titanium dioxide (E171) and purified water.

What Donepezil hydrochloride looks like and contents of the pack

Donepezil hydrochloride 5 mg, film-coated tablets

Donepezil hydrochloride 5 mg, film-coated tablets are white to-off-white, round film-coated tablets, blistered with 14 on one side and 8 on the other side.

Donepezil hydrochloride 10 mg, film-coated tablets

Donepezil hydrochloride 10 mg, film-coated tablets are white to-off-white, round film-coated tablets, blistered with 7 on one side and 10 on the other side.

The film-coated tablets are available in blisters of 28, 50, 90, 100 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Mylan Pharmaceuticals UK Ltd

Acros Business Park

Gentemperepark 22 – Black C

9869 Helftense

Hemiksem

Manufacturers:

Pfizer supply

Acros Business Park

Gentemperepark 22 – Black C

9869 Helftense

Hemiksem

Belgium

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