

**Donepezil hydrochloride 5mg film-coated tablets
(Donepezil hydrochloride)
PL 14894/0479**

**Donepezil hydrochloride 10mg film-coated tablets
(Donepezil hydrochloride)
PL 14894/0480**

UK Public Assessment Report

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Donepezil hydrochloride 5mg film-coated tablets**(Donepezil hydrochloride)****PL 14894/0479****Donepezil hydrochloride 10mg film-coated tablets****(Donepezil hydrochloride)****PL 14894/0480****LAY SUMMARY**

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Ranbaxy UK Limited Marketing Authorisations (licences) for the medicinal products Donepezil hydrochloride 5mg film-coated tablets (PL 14894/0479) and Donepezil hydrochloride 10mg film-coated tablets (PL 14894/0480) on 30th June 2008. These are prescription-only medicines (POM) used for the treatment of the symptoms of dementia – a general decline in all areas of mental ability such as memory, concentration, and judgement in people diagnosed as having Alzheimer’s Disease.

These medicinal products contain the active ingredient Donepezil hydrochloride, which belongs to a group of medicines called acetylcholinesterase inhibitors.

The test products were considered to be the same as the reference products Aricept Tablets 5mg and Aricept Tablets 10mg (PL 10555/0006 & 0007, Eisai Co Ltd) based on the data submitted by Ranbaxy UK Limited.

These applications are based on reference products with valid UK licences. No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Donepezil hydrochloride 5mg film-coated tablets and Donepezil hydrochloride 10mg film-coated tablets outweigh the risks; hence Marketing Authorisations (MAs) have been granted.

**Donepezil hydrochloride 5mg 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 MHRA granted Ranbaxy UK Limited Marketing Authorisations for the medicinal products Donepezil hydrochloride 5mg film-coated tablets (PL 14894/0479) and Donepezil hydrochloride 10mg film-coated tablets (PL 14894/0480) on 30th June 2008. The products are prescription-only medicines.

These are abridged applications for Donepezil hydrochloride 5mg film-coated tablets and Donepezil hydrochloride 10mg film-coated tablets. These are two strengths of Donepezil, submitted under Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of the reference products Aricept Tablets 5mg and Aricept Tablets 10mg (PL 10555/0006 & 0007) respectively, granted to Eisai Co Ltd on 14/02/1997. The reference products have been authorised in the UK for more than 10 years, so the period of data exclusivity has expired.

Donepezil hydrochloride 5mg and 10mg film-coated tablets contain the active ingredient donepezil, which is a drug for dementia. The products are indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia.

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

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.

These applications for Donepezil hydrochloride 5mg and 10mg film-coated tablets were submitted at the same time and both depend on the bioequivalence study presented comparing the applicant's test 10mg strength product with the reference product Aricept 10mg Tablets, manufactured by Laboratoire Pfizer, France. Consequently, all sections of the Scientific Discussion refer to both products.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

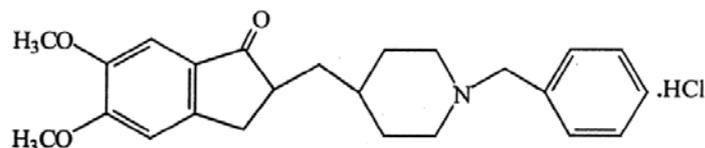
Donepezil hydrochloride

Nomenclature:

INN: Donepezil hydrochloride

Chemical name: 2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1*H*-inden-1-one hydrochloride

Structure:



Molecular formula: $C_{24}H_{29}NO_3 \cdot HCl$

Molecular weight: 415.96

Physical form: White to off-white crystalline powder

Solubility: Soluble in chloroform, sparingly soluble in water, methanol and acetic acid

The active substance, donepezil hydrochloride, is not the subject of a European Pharmacopoeia (EP) monograph.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal or biological origin, and therefore comply with the TSE requirements.

An appropriate specification has been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for reference standards used by the active substance manufacturer during validation studies.

Active donepezil hydrochloride is stored in appropriate packaging. It is packed into a triple polybag which is placed inside a HDPE drum / container. The triple polybag consists of a low-density polyethylene (LDPE) bag as the primary inner bag; a middle bag (blend of High Molecular Weight High Density Polyethylene (HMHDPE), LDPE and Linear Low Density Polyethylene (LLDPE)); and an outer bag (polyester film / aluminium foil / LDPE). Specifications and Certificates of Analysis have been provided for the packaging materials used. The LDPE inner bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in the proposed packaging. These data demonstrate the stability of the active substance and support a retest period of 36 months when stored in the proposed packaging.

DRUG PRODUCT

Description and Composition

Donepezil hydrochloride 5mg film-coated tablets are yellow coloured, circular, biconvex film coated tablets debossed with 'RC25' on one side. Donepezil hydrochloride 10mg film-coated tablets are yellow coloured, capsule shaped, film coated tablets debossed with 'RC' & '26' on either side of the breakline on one side and a breakline on the other side.

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, maize starch, hydroxypropyl cellulose, microcrystalline cellulose, sodium starch glycolate-type A, magnesium stearate, and Opadry 02B52480 Yellow - containing hypromellose 5cP, titanium dioxide (E171), macrogol, talc and iron oxide yellow (E172). Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monograph, apart from Opadry 02B52480 Yellow, which complies with satisfactory in-house specifications. All the constituents of Opadry 02B52480 Yellow comply with their respective European Pharmacopoeia monograph, apart from Iron oxide yellow (E172) which complies with the national formulary (NF). Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate is of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

There were no novel excipients used and no overages.

Dissolution and impurity profiles

Dissolution profiles for the applicant's test products (Donepezil hydrochloride 5mg and 10mg film-coated tablets) were found to be similar to those for the EU reference products (Aricept 10mg tablets – Pfizer, France & Pfizer, Finland), and were satisfactory.

Comparative impurity data were presented for Donepezil hydrochloride 5mg and 10mg film-coated tablets, and the EU reference products (Aricept 5mg tablets and Aricept 10mg tablets – Pfizer, France & Pfizer, Finland). Impurity profiles for the drug product were found to be similar to those for the EU reference products, and all the impurities are within the specification limits.

Pharmaceutical development

Details of the pharmaceutical development of the drug products have been supplied and are satisfactory.

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 studies have been conducted and are satisfactory.

Finished product specification

The finished product specifications proposed for both release and shelf life are acceptable, and provide an assurance of the quality and consistency of the finished products. 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 reference standards used.

Container Closure System

The tablets are packaged in 'Bulk shipment packs' for transportation and repackaging in the EU. One of these packs comprises of 10,000 tablets of 5mg or 5,000 tablets of 10mg with 3 desiccant sachets of 10 g in a polybag. One such polybag is further packed in a triple laminated bag along with 2 desiccant sachets of 10 g, and sealed.

The finished product is marketed in PVC (polyvinylchloride) / aluminium or PVC (polyvinylchloride) / PVdC (polyvinylidene chloride) / aluminium blister strips, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The product is packaged in carton pack sizes of 28 film-coated tablets.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been set for the marketed packs, which is satisfactory. There are no specific storage instructions.

A simulated bulk shipment pack has been assessed for stability, and a 12 months holding time is considered acceptable.

Bioequivalence Study

A bioequivalence study was presented comparing the test product, Donepezil hydrochloride 10mg film-coated tablets, to the reference product, Aricept 10mg tablets (manufactured by Laboratoire Pfizer, France).

An evaluation of the bioequivalence study is found in the Clinical Assessment section.

Expert Report

A satisfactory expert report is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

Product Information

The approved SmPCs, leaflet, and labelling are satisfactory. Colour mock-ups of the labelling have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

Conclusion

The test products are pharmaceutically equivalent to the reference products which have been licensed in the UK for over 10 years. The drug products correspond to the current EU definition of a generic medicinal product because they comply with the criteria of having the same qualitative and quantitative composition in terms of the active substance and pharmaceutical form. On this basis, and considering the bioequivalence data provided, the applicant's claim that Donepezil hydrochloride 10mg film-coated tablets are a generic medicinal product of Aricept 10mg tablets appears justified.

As Donepezil hydrochloride 5mg and 10mg film-coated tablets meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 10mg strength were extrapolated to the 5mg strength product.

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. Marketing Authorisations were, therefore, granted.

PRECLINICAL ASSESSMENT

These abridged applications for Donepezil hydrochloride 5mg and 10mg film-coated tablets were submitted according to Article 10.1 of Directive 2001/83/EC, as amended.

No new preclinical data have been supplied with these applications and none are required for applications of this type. A preclinical expert report has been written by a suitably qualified person and is satisfactory.

CLINICAL ASSESSMENT

INDICATIONS

Donepezil hydrochloride 5mg and 10mg film-coated tablets are indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia.

The indications are identical to those for the innovator product and are satisfactory.

POSODOLOGY AND METHOD OF ADMINISTRATION

The posology is consistent with that for the innovator product and is satisfactory.

TOXICOLOGY

No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY

Pharmacodynamics

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 which 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 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 cannot be considered to have any effect on the progress of the disease.

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

Pharmacokinetics

Absorption: Maximum plasma levels are reached approximately 3 to 4 hours after oral administration. The terminal disposition half-life is approximately 70 hours. Approximate steady-state is achieved within 3 weeks after initiation of therapy. 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, studies suggest 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.

Bioequivalence study

The applicant presented a single bioequivalence study comparing the test product, Donepezil hydrochloride 10mg film-coated tablets, to the reference product, Aricept 10mg tablets (Laboratoire Pfizer, France). The study was of an appropriate design and was conducted to principles of Good Clinical Practice.

The study was an open label, balanced, randomised, two-treatment, two-period, two-sequence, single-dose, crossover design conducted in 26 healthy, adult, male, human subjects under fasting conditions.

A single oral dose of Donepezil Hydrochloride 10 mg of either test or reference was administered during each period of the study, following a controlled period of fasting. The 26 enrolled subjects were randomized to receive the assigned medication. Subject No. 02 was withdrawn prior to dosing in Period I, due to abnormally high blood pressure. Hence, the test and reference products were administered to 13 and 12 subjects respectively in Period I. A wash out period of 35 days was allowed between dosing. In Period II, the test and reference products were administered to 9 subjects each due to drop outs. A total of 16 subjects completed both periods of the study.

Blood samples were collected pre-dose and at 0.5, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 7, 9, 12, 24, 48, and 72 hours post-dose in each period. The pre-dose blood sample in each period was collected in duplicate (2 x 5 ml), within a period of 1.5 hours before dosing. Post-dose samples were generally collected within 2 minutes of the scheduled time.

Plasma samples were analysed for donepezil, 6-desmethyl donepezil and 5-desmethyldonepezil by LC-MS/MS. The lower limits of quantification were 0.339, 0.100 and 0.103ng/ml for donepezil, 6-desmethyl- and 5-desmethyldonepezil respectively. The method was validated and the validation report was provided.

Statistical evaluation was performed for $AUC_{(0-t)}$ and C_{max} with ANOVA and the 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated.

PARAMETER	RATIO T/R (%)	90% CI
AUC_{0-72}	103.50	97.89-109.43
C_{max}	102.13	93.50-111.56

Statistical evaluation confirmed that the pharmacokinetics of the reference and test products were sufficiently similar to enable a conclusion of bioequivalence. The point estimates for the log- (natural) -transformed data for C_{max} and AUC_{0-72} for donepezil were 102.13% and 103.50%, respectively.

The 90% confidence intervals for the parameters C_{max} and AUC_{0-72} were within the CPMP acceptance criteria of 80-125 % for inferring bioequivalence between Donepezil hydrochloride 10mg film-coated tablets and Aricept 10mg tablets (Laboratoire Pfizer, France).

EFFICACY

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

Efficacy is reviewed in the Clinical Expert Report. The reference products are established and the applications depend upon the bioequivalence study.

SAFETY

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

Safety is reviewed in the Clinical Expert Report. The reference products are established and the applications depend upon the bioequivalence study.

EXPERT REPORT

A satisfactory expert report is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

PRODUCT INFORMATION:**Summary of Product Characteristics (SmPC)**

The approved SmPCs are consistent with those for the reference products and are acceptable.

Patient Information Leaflet (PIL)

The PIL is in line with the approved SmPCs and is satisfactory.

Labelling

The labelling is satisfactory.

CONCLUSIONS

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test (Donepezil hydrochloride 10mg film-coated tablets) and reference (Aricept 10mg tablets) products within general acceptance limits. The results and conclusions of the bioequivalence study on the 10mg strength were extrapolated to the 5mg strength product. Therefore, it can be concluded that the 5mg strength donepezil formulation is bioequivalent to its corresponding marketed brand formulation, despite bioequivalence not being assessed explicitly.

Sufficient clinical information has been submitted to support these applications. Marketing Authorisations were, therefore, recommended to be granted on medical grounds.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Donepezil hydrochloride 5mg and 10mg 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

Bioequivalence has been demonstrated between the applicant's Donepezil hydrochloride 10mg film-coated tablets, and the reference product Aricept 10mg tablets (Laboratoire Pfizer, France). As the applicant's products were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 10mg strength were extrapolated to the 5mg tablet strength. Thus, no separate bioequivalence study was necessary for the 5mg strength.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory and consistent with those for Aricept 5mg tablets and Aricept 10mg tablets.

A package leaflet has been 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 it contains.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study, and the valid extrapolation of its results and conclusions, support the claim that the applicant's products and their respective reference products are interchangeable. Extensive clinical experience with donepezil hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

Donepezil hydrochloride 5mg film-coated tablets
(Donepezil hydrochloride)
PL 14894/0479

Donepezil hydrochloride 10mg film-coated tablets
(Donepezil hydrochloride)
PL 14894/0480

STEPS TAKEN FOR ASSESSMENT

- 1 The MHRA received the marketing authorisation applications on 8th October 2006.
- 2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 19th January 2007.
- 3 Following assessment of the applications, the MHRA requested further information relating to the clinical dossiers on 24th January 2007, and further information relating to the quality dossiers on 5th June 2007.
- 4 The applicant responded to the MHRA's requests, providing further information for the clinical sections on 19th February 2007, and further information for the quality sections on 24th August 2007
- 5 The applications were determined on 30th June 2008

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Donepezil hydrochloride 5mg film-coated Tablets is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Donepezil Hydrochloride 5 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5mg Donepezil Hydrochloride (equivalent to 4.56mg of Donepezil)

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film Coated

Yellow coloured, circular, biconvex film coated tablets debossed with 'RC25' on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Donepezil Hydrochloride tablets are 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 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. The dose of Donepezil Hydrochloride can be increased to 10 mg/day (once-a-day dosing). The maximum recommended daily dose is 10 mg. Upon discontinuation of treatment, a gradual abatement of the beneficial effects of Donepezil Hydrochloride is seen. There is no evidence of a rebound effect after abrupt discontinuation of therapy.

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:

Donepezil Hydrochloride is not recommended for use in children.

4.3 Contraindications

Donepezil Hydrochloride is contraindicated in patients with a known hypersensitivity to Donepezil Hydrochloride, piperidine derivatives, or to any excipients used in the formulation. Donepezil Hydrochloride is contraindicated in pregnancy. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

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. 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 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 nonsteroidal anti-inflammatory drugs (NSAIDs), should be monitored for symptoms.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Donepezil hydrochloride and/or any of its metabolites does not inhibit the metabolism of theophylline, warfarin, cimetidine or digoxin in humans. The metabolism of donepezil hydrochloride is not affected by concurrent administration of digoxin or cimetidine. In vitro studies have shown that the cytochrome P450 isoenzymes 3A4 and to a minor extent 2D6 are involved in the metabolism of donepezil. Drug interaction studies performed in vitro show that ketoconazole and quinidine, inhibitors of CYP3A4 and 2D6 respectively, inhibit donepezil metabolism. Therefore these and other CYP3A4 inhibitors, such as itraconazole and erythromycin, and CYP2D6 inhibitors, such as fluoxetine could inhibit the metabolism of donepezil. In a study in healthy volunteers, ketoconazole increased mean donepezil concentrations by about 30%. Enzyme inducers, such as rifampicin, phenytoin, carbamazepine and alcohol may reduce the levels of donepezil. Since the magnitude of an inhibiting or inducing effect is unknown, such drug combinations should be used with care. Donepezil hydrochloride has the potential to interfere with medications having anticholinergic activity. There is also the potential for synergistic activity with concomitant treatment involving medications such as succinylcholine, other neuro-muscular blocking agents or cholinergic agonists or beta blocking agents which have effects on cardiac conduction.

4.6 Pregnancy and lactation

Pregnancy:

Teratology 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 evidence for a teratogenic potential. 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 effect was observed at the next lower dose tested, approximately 15 times the human dose. Donepezil should not be used during pregnancy. For donepezil no clinical data on exposed pregnancies are available.

Lactation:

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

4.7 Effects on ability to drive and use machines

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

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: common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100) and rare >1/10,000, <1/1,000).

System Organ Class	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 Vomiting Nausea Abdominal disturbance	Gastrointestinal haemorrhage Gastric and duodenal ulcers	

Hepato-biliary disorders			Liver dysfunction including hepatitis***
Skin and subcutaneous tissue disorders	Rash		
	Pruritis		
Musculoskeletal, connective tissue and bone disorders	Muscle cramps		
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 and poisoning	Accident		

*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 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.

Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.

As in any case of overdose, general supportive measures should be utilised. Tertiary anticholinergics such as atropine may be used as an antidote for Donepezil Hydrochloride overdosage. Intravenous atropine sulphate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether donepezil hydrochloride and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The pharmacotherapeutic group: drugs for dementia; 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 which 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 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 cannot be considered to have any effect on the progress of the disease.

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

5.2 Pharmacokinetic properties

General characteristics

Absorption: Maximum plasma levels are reached approximately 3 to 4 hours after oral administration. Plasma concentrations and area under the curve rise in proportion to the dose. The terminal disposition half-life is approximately 70 hours, thus, administration of multiple single-daily doses results in gradual approach to steady-state. Approximate steady-state is achieved within 3 weeks after initiation of therapy. Once at steady-state, plasma donepezil hydrochloride concentrations and the related pharmacodynamic activity show little variability over the course of the day.

Food did not affect the absorption of donepezil hydrochloride.

Distribution: Donepezil hydrochloride is approximately 95% bound to human plasma proteins. The plasma protein binding of the active metabolite 6-O-desmethyldonepezil is not known. The distribution of donepezil hydrochloride in various body tissues has not been definitively studied. However, in a mass balance study conducted in healthy male volunteers, 240 hours after the administration of a single 5 mg dose of ¹⁴C-labelled donepezil hydrochloride, approximately 28% of the label remained unrecovered. This suggests that donepezil hydrochloride and/or its metabolites may persist in the body for more than 10 days.

Metabolism/Excretion: Donepezil hydrochloride is both excreted in the urine intact and metabolised by the cytochrome P450 system to multiple metabolites, not all of which have been identified. Following administration of a single 5 mg dose of ¹⁴C-labeled 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 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 above). 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 above).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate,
Maize starch,
Hydroxypropyl cellulose,
Microcrystalline cellulose,
Sodium starch glycolate-type A,
Magnesium stearate

Opadry 02B52480 Yellow containing: Hypromellose 5cP, (E464)
Titanium dioxide, (E171)
Macrogol,
Talc,
Iron oxide yellow (E172)

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

Blister pack of PVC/Aluminum foil

Or

Blister pack of PVC/PVdC/Al

Pack sizes: 28 tablets

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Ranbaxy (UK) Limited
20 Balderton street
London
W1K – 6TL

8 MARKETING AUTHORISATION NUMBER(S)

PL 14894/0479

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/06/2008

10 DATE OF REVISION OF THE TEXT

22/08/2008

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Donepezil hydrochloride 10mg film-coated Tablets is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Donepezil Hydrochloride 10 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10mg Donepezil Hydrochloride (equivalent to 9.12mg of Donepezil)

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film Coated tablet

Yellow coloured, capsule shaped, film coated debossed with 'RC' and 26 on either side of the breakline on one side and a breakline on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Donepezil Hydrochloride tablets are 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 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. The dose of Donepezil Hydrochloride can be increased to 10 mg/day (once-a-day dosing). The maximum recommended daily dose is 10 mg. Upon discontinuation of treatment, a gradual abatement of the beneficial effects of Donepezil Hydrochloride is seen. There is no evidence of a rebound effect after abrupt discontinuation of therapy.

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:

Donepezil Hydrochloride is not recommended for use in children.

4.3 Contraindications

Donepezil Hydrochloride is contraindicated in patients with a known hypersensitivity to Donepezil Hydrochloride, piperidine derivatives, or to any excipients used in the formulation. Donepezil Hydrochloride is contraindicated in pregnancy. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

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. 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 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 nonsteroidal anti-inflammatory drugs (NSAIDs), should be monitored for symptoms.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Donepezil hydrochloride and/or any of its metabolites does not inhibit the metabolism of theophylline, warfarin, cimetidine or digoxin in humans. The metabolism of donepezil hydrochloride is not affected by concurrent administration of digoxin or cimetidine. In vitro studies have shown that the cytochrome P450 isoenzymes 3A4 and to a minor extent 2D6 are involved in the metabolism of donepezil. Drug interaction studies performed in vitro show that ketoconazole and quinidine, inhibitors of CYP3A4 and 2D6 respectively, inhibit donepezil metabolism. Therefore these and other CYP3A4 inhibitors, such as itraconazole and erythromycin, and CYP2D6 inhibitors, such as fluoxetine could inhibit the metabolism of donepezil. In a study in healthy volunteers, ketoconazole increased mean donepezil concentrations by about 30%. Enzyme inducers, such as rifampicin, phenytoin, carbamazepine and alcohol may reduce the levels of donepezil. Since the magnitude of an inhibiting or inducing effect is unknown, such drug combinations should be used with care. Donepezil hydrochloride has the potential to interfere with medications having anticholinergic activity. There is also the potential for synergistic activity with concomitant treatment involving medications such as succinylcholine, other neuro-muscular blocking agents or cholinergic agonists or beta blocking agents which have effects on cardiac conduction.

4.6 Pregnancy and lactation

Pregnancy:

Teratology 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 evidence for a teratogenic potential. 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 effect was observed at the next lower dose tested, approximately 15 times the human dose. Donepezil should not be used during pregnancy. For donepezil no clinical data on exposed pregnancies are available.

Lactation:

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

4.7 Effects on ability to drive and use machines

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

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: common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100) and rare >1/10,000, <1/1,000).

System Organ Class	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	Gastrointestinal	

	Vomiting Nausea Abdominal disturbance	haemorrhage Gastric and duodenal ulcers	
Hepato-biliary disorders			Liver dysfunction including hepatitis***
Skin and subcutaneous tissue disorders	Rash Pruritis		
Musculoskeletal, connective tissue and bone disorders	Muscle cramps		
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 and poisoning	Accident		

*In investigating patients for syncope or seizure the possibility of heart block or long sinusal pauses should be considered (see section 4.4)

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

***In cases of unexplained liver dysfunction, withdrawal of Donepezil 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.

Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.

As in any case of overdose, general supportive measures should be utilised. Tertiary anticholinergics such as atropine may be used as an antidote for 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 (hemodialysis, peritoneal dialysis, or hemofiltration).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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General characteristics

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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 above).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate,
Maize starch,
Hydroxypropyl cellulose,
Microcrystalline cellulose,
Sodium starch glycolate-type A,
Magnesium stearate

Opadry 02B52480 Yellow containing: Hypromellose 5cP, (E464)
Titanium dioxide, (E171)
Macrogol,
Talc,
Iron oxide yellow (E172)

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

Blister pack of PVC/Aluminum foil

Or

Blister pack of PVC/PVdC/Al

Pack sizes: 28 tablets

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Ranbaxy (UK) Limited
20 Balderton street
London
W1K – 6TL

8 MARKETING AUTHORISATION NUMBER(S)

PL 14894/0480

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/06/2008

10 DATE OF REVISION OF THE TEXT

22/08/2008

PATIENT INFORMATION LEAFLET



PATIENT INFORMATION LEAFLET

Donepezil hydrochloride 5mg Film-coated tablets Donepezil hydrochloride 10mg Film-coated tablets

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

- *Keep this leaflet. You may need to read it again.*
- *If you have further questions, please ask your doctor or your pharmacist.*
- *This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.*

In this leaflet:

1. **What Donepezil hydrochloride 5/10mg Film-coated tablets are and what are they used for**
2. **Before you take Donepezil hydrochloride 5/10mg Film-coated tablets**
3. **How to take Donepezil hydrochloride 5/10mg Film-coated tablets**
4. **Possible side effects**
5. **Storing Donepezil hydrochloride 5/10mg Film-coated tablets**
6. **Further Information**

1. WHAT Donepezil hydrochloride 5/10 mg Film-coated TABLETS ARE AND WHAT ARE THEY USED FOR

Donepezil hydrochloride film-coated tablets belong to a group of medicines called acetylcholinesterase inhibitors. It is used to treat the symptoms of dementia a general decline in all areas of mental ability such as memory, concentration, and judgement in people diagnosed as having Alzheimer's Disease.

statements were applicable to you at any time in the past.

Taking other medicines

Care is needed if you are taking:

- Ketoconazole or itraconazole (anti-fungal medications); erythromycin (antibiotic); fluoxetine (medication used in patients with depression); quinidine.
- Rifampicin; phenytoin or carbamazepine (anti-seizure medications); alcohol
- Medicines to treating high blood pressure and certain heart conditions such as beta blockers (e.g. atenolol, metoprolol).
- Succinylcholine (muscle relaxant)

Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicines, even those not prescribed but bought / obtained without a prescription.

Pregnancy and breast-feeding

If you are pregnant, trying to become pregnant or breast-feeding please consult your doctor before taking this medicine.

Driving and using machines

Donepezil hydrochloride can cause dizziness, fatigue and muscle cramps. This may impair your ability to concentrate and react. You should not plan to drive or operate dangerous machinery until you are sure that this does not affect you.

Important information about some of the ingredients of Donepezil hydrochloride film-coated tablets

Your medicine contains small quantities of an inactive ingredient known as lactose monohydrate.

2. BEFORE YOU TAKE Donepezil hydrochloride 5/10mg Film-coated TABLETS

Do not take Donepezil hydrochloride 5/10 mg film-coated tablets if any of the following apply to you

- You have previously had an allergic reaction to donepezil or to any of the other ingredients of Donepezil hydrochloride tablets (An allergic reaction may include rash, itching, swelling of face, lips, or hands/feet, or breathing difficulties)
- You are pregnant or breast feeding

If you think any of these apply to you, do not take the tablets, talk to your doctor and follow the advice given.

Take special care with Donepezil hydrochloride 5/10mg Film-coated tablets if

- you have markedly reduced liver functions
- you have a history of stomach ulcers
- you are taking NSAID's (group of medicines called non-steroidal anti-inflammatory drugs, which are used to reduce inflammation and pain in the joints and muscles)
- you have difficulty passing urine
- you ever had a seizure
- you have asthma or other long term lung disease
- you have a heart condition
- you are planning to have an operation

Please consult your doctor, even if these

If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE Donepezil hydrochloride 5/10mg Film-coated TABLETS

Dosage

Always take Donepezil hydrochloride film-coated tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Method of administration

Donepezil hydrochloride film-coated tablets should only be taken orally with water at night before you go to bed.

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

To help you remember to take your medicine, try to get into the habit of taking it at the same time each day.

You should never take more than 10 mg of Donepezil hydrochloride on any single day (24 hours).

Donepezil hydrochloride 5/10mg Film-coated tablets are not recommended for children.

Patients with impaired liver

Your dose may be different in case you have a problem with your liver.

Treatment duration

Take your Donepezil hydrochloride film-coated tablets as directed and for as long as directed; do not stop them, even if you feel better, as otherwise the symptoms may return. You will need to see your doctor from time to time to review your treatment and assess your symptoms.

If you have the impression that the effect of Donepezil hydrochloride film-coated tablets is too strong or too weak, talk to your doctor or pharmacist.

If you forget to take Donepezil hydrochloride film-coated tablets at the right time, take them as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take a double dose to make up for forgotten individual doses.

If you have taken more Donepezil hydrochloride film-coated tablets than you should, consult your doctor or go to the nearest hospital casualty department immediately. Take this leaflet or some tablets with you so your doctor will know what you have taken.

If you want to stop taking Donepezil hydrochloride:

Do not stop taking Donepezil hydrochloride without consulting your doctor as your symptoms may return.

4. POSSIBLE SIDE EFFECTS

Like all medicines, **Donepezil hydrochloride film-coated tablets** can cause side effects.

bulging muscle), lack of sleep, general tiredness or weakness, headache

- Itching, rash
- Inability to hold urine
- Common cold
- Anorexia
- Insomnia
- General fatigue and pain

There may be changes in the results of certain laboratory tests

- Abnormal liver function tests
- Increase in serum concentration of muscle creatine kinase

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING DONEPEZIL HYDROCHLORIDE film-coated tablets

Keep out of the sight and reach of children. Do not take after the expiry date that is printed on the packaging. Store in the original package.

If your doctor tells you to stop taking the tablets, please take them back to the pharmacist

6. FURTHER INFORMATION

The name of your medicine is **Donepezil hydrochloride 5/10mg Film-coated tablets** referred to as Donepezil hydrochloride film-coated tablets or Donepezil hydrochloride throughout this leaflet. Donepezil hydrochloride film-coated tablets are available in two strengths: 5 mg and 10 mg.

If any of the following happen, stop taking **Donepezil hydrochloride film-coated tablets** and tell your doctor immediately, or go to the casualty department at your nearest hospital:

- Allergic reaction to Donepezil hydrochloride (An allergic reaction may include rashes, hives, itching, chest constriction, shortness of breath or swelling of face, lips, hands / feet, fever, fainting)

You may need urgent medical attention or hospitalization.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

- Hallucinations (false or distorted sensory experiences that appear to be real perceptions. These sensory impressions are generated by the mind rather than by any external stimuli, and may be seen, heard, felt, and even smelled or tasted), aggressive behavior, agitation
- Seizure/fits; feel dizzy or faint, especially when you stand up suddenly; shaking, stiffness or uncontrollable movement especially of the face and tongue but also of the limbs
- Heart conditions for example slow heart beat
- Any sign of bleeding in the stomach or intestine, e.g. vomiting blood or bowel motions with signs of blood, stomach ulcers
- Liver disorders including hepatitis (yellowing of skin and whites of eyes with decreased appetite, abdominal pain)

Other side effects that may occur and should be reported to your doctor:

- Nausea (feeling sick), vomiting (being sick), stomach pain, diarrhoea (loose stools), loss of appetite
- Muscle cramps (painful contractions of the muscles which produce a hard,

What Donepezil hydrochloride film-coated tablets contains:

The active substance is donepezil hydrochloride.

Donepezil hydrochloride also contain some inactive ingredients: these are Lactose monohydrate, Maize starch, Hydroxypropyl cellulose, Microcrystalline cellulose, Sodium starch glycolate, Magnesium stearate

What Donepezil hydrochloride looks like and contents of the pack:

Donepezil hydrochloride 5mg film-coated tablets are yellow coloured, circular, biconvex film coated tablets debossed with 'RC25' on one side

Donepezil hydrochloride 10mg film-coated tablets are yellow coloured, circular, capsule shaped film coated tablets debossed with 'RC' & '26' on either side of the breakline on one side and a breakline on the other side

Film coating on the tablet Opadry yellow contains Hypromellose 5cP, Titanium dioxide, Macrogol, Talc, Iron Oxide Yellow

Donepezil hydrochloride 5/10mg Film-coated tablets are available as strip packs of 28 tablets.

Marketing Authorisation Holder: Ranbaxy (UK) Ltd, 20 Balderton Street, London, W1K 6TL

Manufacturer: Ranbaxy Ireland Limited, Spafield, Cork Road, Cashel, Co-Tipperary, Republic of Ireland

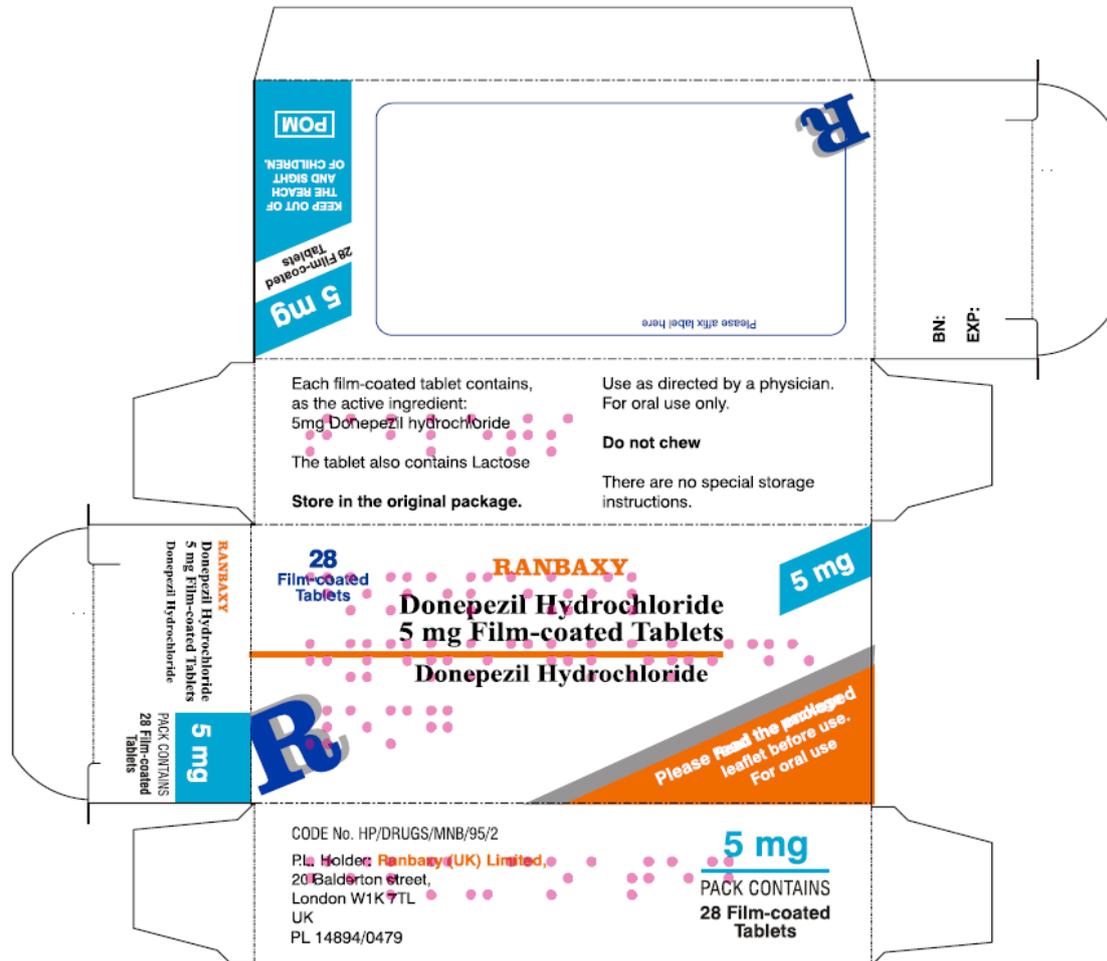
This leaflet was prepared in August 2008.

RANBAXY

LABELLING

Donepezil hydrochloride 5mg film-coated tablets

Carton with Braille



Translation of Braille

Donepezil
hydrochloride
5mg
Film-coated
tablets

Blister foils

Donepezil hydrochloride 5mg film-coated tablets

<p>RANBAXY Donepezil Hydrochloride 5 mg Film-coated Tablets P.L. Holder: Ranbaxy (UK) Limited</p>	<p>RANBAXY Donepezil Hydrochloride 5 mg Film-coated Tablets P.L. Holder: Ranbaxy (UK) Limited</p>	<p>CODE No.: HP/DRUGS/MNB/95/2</p>
<p>Press the tablet through foil from the other side.</p>		
<p>RANBAXY Donepezil Hydrochloride 5 mg Film-coated Tablets P.L. Holder: Ranbaxy (UK) Limited</p>	<p>RANBAXY Donepezil Hydrochloride 5 mg Film-coated Tablets P.L. Holder: Ranbaxy (UK) Limited</p>	
<p>Press the tablet through foil from the other side.</p>		<p>CODE No.: HP/DRUGS/MNB/95/2</p>
<p>RANBAXY Donepezil Hydrochloride 5 mg Film-coated Tablets P.L. Holder: Ranbaxy (UK) Limited</p>	<p>RANBAXY Donepezil Hydrochloride 5 mg Film-coated Tablets P.L. Holder: Ranbaxy (UK) Limited</p>	
<p>Press the tablet through foil from the other side.</p>		

Donepezil hydrochloride 10mg film-coated tablets

<p>RANBAXY Donepezil Hydrochloride 10 mg Film-coated Tablets P.L. Holder: Ranbaxy (UK) Limited</p>	<p>RANBAXY Donepezil Hydrochloride 10 mg Film-coated Tablets P.L. Holder: Ranbaxy (UK) Limited</p>	<p>CODE No.: HP/DRUGS/MNB/95/2</p>
<p>Press the tablet through foil from the other side.</p>		
<p>RANBAXY Donepezil Hydrochloride 10 mg Film-coated Tablets P.L. Holder: Ranbaxy (UK) Limited</p>	<p>RANBAXY Donepezil Hydrochloride 10 mg Film-coated Tablets P.L. Holder: Ranbaxy (UK) Limited</p>	
<p>Press the tablet through foil from the other side.</p>		<p>CODE No.: HP/DRUGS/MNB/95/2</p>
<p>RANBAXY Donepezil Hydrochloride 10 mg Film-coated Tablets P.L. Holder: Ranbaxy (UK) Limited</p>	<p>RANBAXY Donepezil Hydrochloride 10 mg Film-coated Tablets P.L. Holder: Ranbaxy (UK) Limited</p>	
<p>Press the tablet through foil from the other side.</p>		