New Zealand Datasheet

1 PRODUCT NAME

Donepezil

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Donepezil hydrochloride 5mg and 10mg tablets.

3 PHARMACEUTICAL FORM

Donepezil film-coated tablets for oral administration are supplied containing 5 mg donepezil hydrochloride, equivalent to 4.56 mg donepezil free base, or 10 mg donepezil hydrochloride, equivalent to 9.12 mg donepezil free base.

Donepezil 5mg tablets are white, circular, biconvex film-coated tablets, embossed 'DPZ' on one side and '5' on the other side. The tablet diameter is approximately 7.1 mm.

Donepezil 10mg tablets are yellow, circular, biconvex film-coated tablets, embossed 'DPZ' on one side and '10' on the other side. The tablet diameter is approximately 9.1 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Donepezil tablets are indicated for the treatment of mild, moderate and severe Alzheimer's disease.

Donepezil tablets are indicated for the treatment of vascular dementia (dementia associated with cerebrovascular disease).

4.2 Dose and method of administration

Adults/Elderly
It is recommended that the diagnosis and treatment of Alzheimer's disease should be initiated and supervised by a doctor with appropriate experience in Alzheimer's disease. Individual patient response to donepezil therapy cannot be predicted.

Where a therapeutic benefit for the patient exists, then treatment should be continued. Where there is no longer evidence of a therapeutic effect, discontinuation of therapy should be considered. The physician should periodically assess the therapeutic effect using input from the patient and caregiver. Donepezil usage in patients with other types of memory impairment (e.g. age-related cognitive decline) or other types of dementia has not been established.

5mg and 10mg dosages of donepezil hydrochloride administered once daily in controlled clinical trials have been shown to be effective. With the 10mg dose per day there is no statistically significant evidence that a greater treatment effect is obtained from this higher dose versus the 5mg/day, however based on analysis of group data there is a suggestion that some additional benefits may accrue to some patients using 10mg/day.

Initial treatment should be started at 5mg/day once a day. Donepezil tablets should be taken in the evening, orally, just prior to retiring. Donepezil tablets can be taken with or without food.

In order to allow the earliest clinical responses to treatment to be assessed and to allow steady-state concentrations of donepezil to be achieved, 5mg/day dosage should be maintained for at least one month. Donepezil tablets can be increased to a dose of 10mg/day (once-a-day dosing) after a one-month clinical assessment of treatment at 5mg/day.

10mg per day is the maximum recommended daily dose. No doses over 10mg per day have been studied in clinical trials.

After discontinuation of treatment using donepezil tablets a gradual abatement of the beneficial effects of donepezil tablets occurs. After abrupt cessation of therapy there is no evidence of any rebound effect.

Renal & Hepatic Impairment
For patients with mild to moderate hepatic or renal impairment, a similar dose schedule can be followed as the clearance of donepezil is not significantly affected by these conditions.

Use in Children
The usage of Donepezil tablets in children is not recommended (see Warnings and Precautions - Paediatric use).

4.3 Contraindications

Any known hypersensitivity to donepezil hydrochloride, piperidine derivatives, or to any of the excipients is a contraindication for Donepezil tablets.

4.4 Special warnings and precautions for use

Anaesthesia
Donepezil hydrochloride may exaggerate succinylcholine-type muscle relaxation during anaesthesia as it is a cholinesterase inhibitor.

Cardiovascular Conditions
Vagotonic effects on heart rate (e.g. bradycardia) may be induced by cholinesterase inhibitors such as donepezil. The potential risk for this action may be increased particularly in patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions, such as atrioventricular or sinoatrial block.

Post-marketing reports show evidence of cardiac conduction conditions which includes QTc interval prolongation, atrioventricular block and Torsade de Pointes (please refer to Section 4.5 Interactions with other medicines and other forms of interactions and Section 4.8 Undesirable effects). Careful monitoring (in some cases, clinical ECG) is required for patients with any pertinent pre-existing cardiac disease, for example, bradyarrhythmias, myocardial infarction recently experienced and uncompensated heart failure, individuals with a family history or with pre-existing QTc interval prolongation, patients who are receiving treatment with medicines concerning the QTc interval, or patients with electrolyte disturbances such as hypomagnesaemia or hypokalaemia.

Gastrointestinal Conditions
Cholinesterase inhibitors such as donepezil will cause an increase in cholinergic activity. This increase in activity may be likely to cause an increase in gastric secretions. The clinical studies with donepezil hydrochloride did not show an increased incidence of either peptic ulcer disease or gastrointestinal bleeding as compared to the placebo. However, patients with certain risk factors such as a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS) may be more likely to develop ulcers. Patients with risk factors should be closely monitored for stomach ulcers, including symptoms of active or occult gastrointestinal bleeding.

Genitourinary
Cholinomimetics may cause bladder outflow obstruction, however this was not observed in clinical trials of donepezil hydrochloride.

Neuroleptic Malignant Syndrome
Neuroleptic Malignant Syndrome (NMS) has been reported in patients treated with donepezil with or without concomitant antipsychotic medication. NMS is a potentially life-threatening condition characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels; additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure.

Neurological Conditions
Cholinomimetics may have some potential to cause generalised convulsions. However, it is difficult to attribute this event to the administration of donepezil alone as seizure activity may also be a manifestation of Alzheimer's disease. Cholinomimetics have the potential to exacerbate or induce extrapyramidal symptoms.

Pulmonary Conditions
Cholinesterase inhibitors such as donepezil should be prescribed with caution to patients with a history of asthma or obstructive pulmonary disease because of their cholinomimetic actions.

The co-administration of other inhibitors of acetylcholinesterase, agonists or antagonists of the cholinergic system and donepezil hydrochloride should be avoided.

Mortality in Subjects with Vascular Dementia
Three clinical trials studying patients meeting the NINDS-AIREN criteria for probable or possible vascular dementia (VaD) and excluding patients with a diagnosis of Alzheimer's disease were conducted for 6 months duration.

In the first study, the mortality rates were 7/199 (3.5%) on placebo, 5/206 (2.4%) on donepezil hydrochloride 10mg, and 2/198 (1.0%) on donepezil hydrochloride 5mg. In the second study, the mortality rates were 1/193 (0.5%) on placebo, 3/215 (1.4%) on donepezil hydrochloride 10mg and 4/208 (1.9%) on donepezil hydrochloride 5mg. In the third study, the mortality rates were 0/326 (0%) on placebo ($p<0.02$), and 11/648 (1.7%) on donepezil hydrochloride 5mg.

For the three VaD studies combined, the mortality rate in the placebo group (1.1%) was smaller numerically than the donepezil hydrochloride group (1.7%) however, there was no significant difference statistically. Various vascular related causes appeared to be the reason for the majority of deaths in patients taking either donepezil hydrochloride or placebo. This is to be expected in the elderly population with underlying vascular disease. There was no difference in the rate of occurrence of all serious non-fatal and fatal vascular events as analysed in the donepezil hydrochloride group relative to placebo.

Mortality in Subjects with Alzheimer's Disease
In the current approved indications of mild, moderate and severe Alzheimer's disease there is no evidence of an increased risk of mortality. When Alzheimer's disease studies were pooled (n=4146), the mortality rate in the placebo group numerically exceeded that in the donepezil hydrochloride group.

Paediatric Use
Donepezil tablets are not recommended for use in children.

4.5 Interaction with other medicines and other forms of interaction

Drugs Highly Bound to Plasma Proteins
In vitro drug displacement studies have been performed between donepezil hydrochloride which is a highly bound drug (96%) and other drugs such as warfarin, frusemide, and digoxin. Donepezil hydrochloride did not affect the binding of warfarin (3µg/mL), frusemide (5µg/mL), digoxin (2ng/mL) to human albumin at donepezil hydrochloride concentrations of 0.3-10µg/mL. Similarly the binding of donepezil hydrochloride to human albumin was not affected by warfarin, frusemide, and digoxin.

Drug-drug Interactions
Reports of Torsade de Pointes and QTc interval prolongation for donepezil have been recorded (please refer to Section 4.4 Special warnings and precautions for use and Section 4.8 Undesirable effects). Caution is recommended and clinical monitoring required in the event donepezil is used concomitantly with other medicines identified to extend the QTc interval. Examples include particular antidepressants (e.g. amitriptyline, citalopram and escitalopram), Class IA antiarrhythmics (e.g. disopyramide), Class III antiarrhythmics (e.g. sotalol and amiodarone), additional antipsychotics (e.g. pimozide, phenothiazine derivatives and ziprasidone) and particular antibiotics (e.g. erythromycin, clarithromycin and moxifloxacin).

Effect of Donepezil Hydrochloride on the Metabolism of Other Drugs
The effect of donepezil hydrochloride on the clearance of other drugs that are also metabolised by CYP 3A4 (e.g. terfenadine, cisapride) or CYP 2D6 (e.g. imipramine) has not been established as there have been no *in vivo* clinical trials. Given the therapeutic plasma concentrations of donepezil (164 nM) with *in vitro* studies and the low rate of binding to these enzymes (mean Ki about 50-130 µM), there is little indication of likelihood of interference. It is not known whether donepezil hydrochloride has any potential for enzyme induction.

No significant effects on the pharmacokinetics of digoxin theophylline, cimetidine or warfarin were observed in formal pharmacokinetic studies evaluating the potential for interactions with donepezil hydrochloride.

Sertraline, thioridazine or risperidone metabolism is not inhibited by donepezil hydrochloride and/or any of its metabolites

Donepezil hydrochloride administered for 21 days in a study of Parkinson's disease patients on optimal treatment with L-dopa/carbidopa, had no effect on L-dopa or carbidopa blood levels. No effects on motor activity were observed in this study.

Effect of Other Drugs on the Metabolism of Donepezil Hydrochloride
Donepezil metabolism *in vitro* is inhibited by ketoconazole and quinidine (which are inhibitors of CYP450, CYP3A4 and CYP2D6, respectively). The cytochrome P450 isoenzymes; CYP3A4 and to a lesser extent CYP2D6 are involved in the metabolism of donepezil during

in vitro studies. These and other CYP2D6 inhibitors (e.g. fluoxetine) and CYP3A4 inhibitors (e.g. erythromycin and itraconazole) could inhibit the metabolism of donepezil.

It is not known if these inhibitors have a clinical effect. In healthy volunteers, in two studies the mean donepezil concentrations increased by about 30% with ketoconazole. These increases are not likely to be clinically relevant and are smaller than those produced by ketoconazole for other agents sharing the CYP3A4 pathway. The pharmacokinetics of ketoconazole was not affected by administration of donepezil.

Inducers of CYP2D6 and CYP3A4 (e.g. carbamazepine phenytoin, rifampicin Phenobarbital, alcohol and dexamethasone) could increase the rate of elimination of donepezil. Such drug combinations that effect this CYP 2D6 and CYP 3A4 pathway should be used with care as the magnitude of inhibition or induction is unknown.

Formal pharmacokinetic studies with donepezil hydrochloride and concurrent administration of digoxin, cimetidine, thioridazine, risperidone or sertraline demonstrated that the metabolism of donepezil hydrochloride is not significantly affected.

With concomitant treatment of donepezil hydrochloride and involving such medications as succinylcholine, other neuro-muscular blocking agents or cholinergic agonists or beta blocking agents which have effects on cardiac conduction, there is also the potential for synergistic activity. However in an *in vitro* study, donepezil hydrochloride had minimal effects on hydrolysis of succinylcholine.

4.6 Fertility, pregnancy and lactation

Pregnancy
No evidence of teratogenic potential of donepezil was found in teratology studies conducted in pregnant rats at doses up to 16 mg/kg/day and in pregnant rabbits at doses up to 10 mg/kg/day. This dose in rats resulted in a systemic drug exposure in excess of human values, however, the extent of systemic drug exposure is not known in the rabbits.

Treatment of pregnant rats with an oral donepezil dose of 10mg/kg/day from late gestation to the end of lactation resulted in a slight increase in incidence of stillborn pups, and slightly reduced pup survival through day 4 postpartum.

In pregnant women, there are no adequate or well-controlled studies. A decision to use donepezil should be made by the physician in pregnancy, only if the potential benefit justifies the potential risk to the foetus.

Breast feeding
Oral treatment of donepezil in nursing rats did show excretion of donepezil and/or its metabolites into milk, with milk concentrations similar to those in plasma. It is not known whether donepezil hydrochloride is excreted in human breast milk and there are no studies in lactating women. Based on the studies of rats, women on donepezil should not breast feed as there is a possibility of donepezil being excreted in milk.

Fertility
In rats up to 10 mg/kg/day donepezil hydrochloride had no effect on fertility. At the maximum recommended human clinical dose of 10 mg/day in male and female rats based on AUC, the rats achieved a tissue exposure equivalent to approximately twice that in humans

4.7 Effects on ability to drive and use machines

Driving performance and the ability to use machinery may be compromised in patients with Alzheimer's disease and vascular dementia. Donepezil can cause muscle cramps, dizziness and fatigue, mainly when initiating or increasing the dose. Patient’s ability to continue driving or operating complex machines of patients should be routinely evaluated by the physician.

4.8 Undesirable effects

Mild to Moderately Severe Alzheimer's Disease Clinical Trials
Most adverse events are mild in severity and transient. The most common (incidence ≥ 5% and twice the frequency of placebo) were diarrhoea, fatigue, insomnia, muscle cramps, nausea and vomiting. Other common adverse events (incidence ≥ 5% and ≥ placebo) were abdominal disturbance, accident, common cold, dizziness, headache and pain. More rarely, cases of atrioventricular block, bradycardia, syncope, and sinoatrial block were observed. Adverse events including asthenia was observed during long-term but not the short-term trials (incidence ≥ 5% and twice the frequency of placebo).

Minor increases in serum concentrations of creatinine kinase were the only observed notable abnormality in laboratory values associated with treatment.

Adverse Events Leading to Discontinuation
The rate of donepezil hydrochloride discontinuation for the 5mg/day treatment group was very similar to that of the placebo group at approximately 5% in clinical trials of mild to moderate Alzheimer’s disease. Treatment discontinuation rate was higher (13%) in patients who received rapid escalations in dose from 5mg/day to 10mg/day over 7 days. Nausea, vomiting and diarrhoea were the most common reasons for discontinuing therapy.

These symptoms were generally mild and transient resolving within 2 days in those patients who did not discontinue therapy and continued usage at the 10 mg/day dose rate. There is evidence to suggest that the rate of titration may affect the frequency of these common adverse events.

Table 1:
In Controlled Clinical Trials of Patients Receiving Donepezil Hydrochloride; Adverse Events Reported in at Least 2% of patients and at a Higher Frequency than Placebo-Treated Patients

Body System/Adverse Event	**Donepezil (n=747)**	**Placebo (n=355)**
Percentage of Patients with any Adverse Event	**74%**	**72%**
Body as a Whole		
Accident	7%	6%
Fatigue	5%	3%
Headache	10%	9%
Pain, various locations	9%	8%
Cardiovascular		
Syncope	2%	1%
Digestive System		
Anorexia	4%	2%
Diarrhoea	10%	5%
Nausea	11%	6%
Vomiting	5%	3%
Haematological and Lymphatic System		
Ecchymosis	4%	3%
Metabolic and Nutritional		
Weight Decrease	3%	1%
Musculoskeletal System		
Arthritis	2%	1%
Muscle Cramps	6%	2%
Body System/Adverse Event (continued)	**Donepezil**	**Placebo**
Nervous System		
Abnormal Dreams	3%	0%
Depression	3%	<1%
Dizziness	8%	6%
Insomnia	9%	6%
Somnolence	2%	<1%
Urogenital		
Frequent urination	2%	1%

Other Adverse Events Observed During Clinical Trials
Clinical investigators recorded signs and symptoms experienced by the patients receiving donepezil using their own terminology. The following summarises adverse events that occurred at least twice, with the exception of those already listed in the previous table and judged to be possibly, or definitely, related to donepezil hydrochloride treatment.

Frequent adverse events: - those occurring in at least 1/100 patients and infrequent adverse events - those occurring in 1/100 to 1/1000 patients are included.

Body as a Whole: infection, generalised weakness, assault, influenza.

Cardiovascular System: angina pectoris, hot flushes, hypertension, hypotension, vasodilation.

Digestive System: abdominal disturbance, bloating, constipation, drooling, dry mouth, epigastric pain, eructation, faecal incontinence, flatulence, gastrointestinal bleeding, increased appetite, stomach upset, increased transaminases.

Metabolic and Nutritional Disorders: oedema of extremities, dehydration.

Musculoskeletal System: weakness in muscles.

Nervous System: abnormal crying, agitation, anxiety, aphasia, ataxia, coldness (localised), confusion, delusions, hallucinations, hypokinesia, irritability, increased libido, muscle spasm, nervousness, paraesthesia, paranoia, restlessness (localised), tremor, aggression, vertigo, wandering.

Respiratory System: coughing, dyspnoea, rhinitis.

Skin and Appendages: abrasion, diaphoresis, puritus, rash.

Special Senses: cataract, ear disorder, vision blurred.

Urogenital System: nocturia, urinary incontinence, urinary tract infection.

Severe Alzheimer's Disease Clinical Trials
In controlled clinical studies, a total of 573 patients with severe Alzheimer's disease were treated with donepezil hydrochloride. Of these patients, 441 (77%) completed the studies. The mean duration of treatment for all donepezil hydrochloride groups was 148.4 days (range 1-231 days).

For severe Alzheimer’s disease the incidence profile for adverse events was similar to that of mild to moderate Alzheimer's disease. The most common adverse events, defined as those occurring at a frequency of at least 5% in patients and twice the placebo rate, were aggression, diarrhoea, and nausea. Other less common adverse events leading to discontinuation included aggression, decreased appetite, diarrhoea, nausea, urinary tract infection, and vomiting.

There were no adverse events occurring in at least 2% of patients and adverse events seen with donepezil hydrochloride therapy numbered twice the incidence seen in placebo patients. In clinical trials the rate of discontinuation in severe Alzheimers due to adverse events was 11.3% in patients treated with donepezil hydrochloride, compared to 6.7% in the placebo group.

Overall, the investigators judged the majority of adverse events to be mild or moderate in intensity.

Vascular Dementia Clinical Trials
The types and relative proportions of adverse events associated with donepezil were similar in the patients with Alzheimer’s disease and vascular dementia in a comparison of the studies. In the combined vascular dementia studies the mortality rate in the placebo group (1.1%) was numerically lower than in the donepezil hydrochloride group (1.7%) (see Warnings and Precautions - Mortality in Subjects with Vascular Dementia).

Post-marketing Experience
Neuroleptic malignant syndrome has been associated with the use of donepezil.

There have also been post-marketing reports of abdominal pain, agitation, aggressive behaviour, cholecystitis, duodenal ulcer, gastric ulcer, gastrointestinal haemorrhage, hallucinations, hepatitis, heart block, haemolytic anaemia, hyponatraemia, pancreatitis seizure and electrocardiogram QT interval prolonged, polymorphic ventricular tachycardia

including Torsade de Pointes. However, there is inadequate data to determine the causal relationship with donepezil hydrochloride.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Animal Study Data
Following administration of a single oral dose in mice, rats and dogs, the estimated median lethal dose of donepezil hydrochloride is 45, 32 and 15mg/kg, respectively, or approximately 225, 160 and 75 times the maximum recommended human dose of 10 mg per day. In animals dose-related signs of cholinergic stimulation were observed and included reduced spontaneous movement, prone position, lacrimation, staggering gait, clonic convulsions, salivation, depressed respiration, fasciculation, lower body surface temperature, and miosis.

Cholinergic Crisis
A cholinergic crisis can result from overdosage with cholinesterase inhibitors. This is characterised by bradycardia, collapse, convulsions, hypotension, respiratory depression, salivation, severe nausea, sweating and vomiting. If respiratory muscles are involved, increased muscle weakness is a possibility and may result in death.

Treatment
General supportive measures should be utilised, as with most overdoses. Donepezil hydrochloride overdosage may be counteracted with tertiary anticholinergics such as atropine. Intravenous atropine sulfate titrated to effect is recommended with an initial dose of 1.0 to 2.0 mg IV with subsequent doses based on clinical response. Co-administration of quarternary anticholinergics (such as glycopyrrolate) with other cholinomimetics has caused atypical responses in blood pressure and heart rate. It is not known whether dialysis (peritoneal dialysis, haemofiltration or haemodialysis) can remove donepezil hydrochloride and/or its metabolites.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-dementia drugs; anticholinesterase; ATC-code N06DA02.

Alzheimer's disease is associated with a relative decrease in cholinergic system activity in the cerebral cortex and other areas of the brain. Donepezil hydrochloride is understood to exert its therapeutic effect in the central nervous system by enhancing cholinergic function. This is accomplished by reversible inhibition of acetylcholine hydrolysis by acetylcholinesterase, which increases the concentration of acetylcholine.

Donepezil hydrochloride was found *in vitro* to be over 1000 times more potent an inhibitor of acetylcholinesterase than of butyrylcholinesterase, an enzyme which is present mainly outside the central nervous system.

Alzheimer's Disease
Administration of 5mg or 10mg of donepezil hydrochloride in single daily doses to patients with Alzheimer's dementia, in clinical trials, produced steady-state inhibition of acetylcholinesterase activity (measured in erythrocyte membranes) of 63.6% and 77.3%, respectively when measured post dose. The donepezil hydrochloride induced inhibition of acetylcholinesterase (AChE) has been shown to correspond closely to the effects in the cerebral cortex. In addition, significant correlation was demonstrated between plasma levels of donepezil hydrochloride, change in ADAS-cog and AChE inhibition. ADAS-cog is a sensitive and well validated scale which examines cognitive performance including attention, language, memory, orientation, praxis and reason.

5.2 Pharmacokinetic properties

Absorption
Donepezil reaches peak plasma concentration in 3 to 4 hours and has a relative oral bioavailability of 100%. Plasma concentrations and the area under the curve rises proportionally according to dose and therefore the oral administration of donepezil produces highly predictable plasma concentrations.

Administration of multiple single-daily doses results in a gradual approach to steady state as the terminal disposition half-life is approximately 70 hours. After initiation of therapy, approximate steady-state is achieved within 3 weeks. Over the course of the day at steady-state, the related pharmacodynamic activity and plasma donepezil hydrochloride concentrations show little variability. The absorption of donepezil hydrochloride is not affected either by time of administration (morning versus evening dose) or by food.

Distribution
Donepezil hydrochloride is approximately 96% bound to human plasma proteins. The steady state volume of distribution is 12L/kg. The donepezil distribution in various body tissues has not been studied definitively. In healthy male volunteers after a single 5mg dose of C^{14}-labeled donepezil hydrochloride in a mass balance study 240 hours after administration, approximately 28% of the label remained un-recovered. Expressed as a percentage of the concentration in plasma, the average CSF:plasma ratio for both doses, was 15.7%. Therefore donepezil and/or its metabolites may persist in the body for more than 10 days.

Metabolism
Donepezil is extensively metabolised into four major metabolites, two of which are known to be active and a number of minor metabolites, not all of which have been identified. Donepezil's three human metabolites have not undergone extensive safety testing in animals. These metabolites comprise an N-oxidation product and two O-demethylated derivatives. Donepezil is metabolised by CYP450 isoenzymes, CYP3A4 and CYP2D6 and undergoes glucuronidation. Donepezil's rate of metabolism is slow and does not appear to be saturable. Formal pharmacokinetic studies are consistent with these results which show that donepezil and/or its metabolites do not inhibit the metabolism of warfarin, theophylline, digoxin, or cimetidine in humans. Concurrent administration of cimetidine or digoxin in pharmacokinetic studies does not affect the metabolism of donepezil. (See Interactions).

Excretion
Donepezil is excreted in the urine intact. Plasma radioactivity expressed as a percent of the administered dose, following administration of C^{14}-labeled donepezil, was present primarily as intact donepezil (53%), 6-O-desmethyl donepezil (11%), which has been reported to inhibit AChE to the same extent as donepezil *in vitro* and was found in the plasma at concentrations equal to about 20% of donepezil.

Over a period of 10 days, approximately 57% of the total radioactivity was recovered in urine and faeces, with about 17% of the donepezil dose recovered in the urine as unchanged, while 28% remained unrecovered. Donepezil plasma concentrations decline with a half-life of approximately 70 hours. There is no evidence to suggest enterohepatic recirculation of donepezil and/or any of its metabolites.

Sex, smoking history and race have no clinically significant influence on plasma concentrations of donepezil.

Pharmacokinetic/dynamic properties
Donepezil in the central nervous system, as an inhibitor of AChE, augments cholinergic function, thereby providing its therapeutic benefit. AChE activity in erythrocyte membranes provides a measurement index for donepezil pharmacodynamics as the enzyme AChE also occurs peripherally in red blood cells. In several human pharmacokinetic/pharmacodynamic controlled clinical trials, this surrogate marker has been evaluated.

In clinical trials the red blood cell AChE inhibition measurements and the population plasma donepezil concentration measurements verified that patients experienced exposure to donepezil hydrochloride and its pharmacodynamic actions as predicted.

There was no apparent relationship from therapeutic drug monitoring shown between plasma concentration and adverse drug reactions.

5.3 Preclinical safety data

Mutagenicity
Following oral administration in rat primary hepatocyte cultures, donepezil did not induce unscheduled DNA synthesis. With *in vitro* assays (bacterial and in the mouse lymphoma forward mutation) donepezil hydrochloride was non mutagenic. In cultures of Chinese hamster lung cell, using the chromosome aberration test, some clastogenic effects were observed in the *in vivo* mouse micronucleus model.

Carcinogenicity
In long-term studies in rats and mice with dietary dosing of donepezil there was no evidence found of carcinogenicity. The mice had peak plasma concentrations of up to 17 times that in humans at the maximum recommended clinical dose of 10 mg/day and the rats had peak plasma concentrations from 6-19 times the maximum human recommended dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Opadry yellow 04F52201
Purified water
Starch.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life is 36 months (3 years) from manufacture.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

Donepezil 5 mg and 10 mg tablets are available in blisters of 90, 100 or 250 tablets.
Not all pack sizes may be available.

6.6 Special precautions for disposal and other handling

Not applicable.

7 MEDICINE SCHEDULE

Prescription Only Medicine.

8 SPONSOR

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9 DATE OF FIRST APPROVAL

12 August 2010

10 DATE OF REVISION OF THE TEXT

19 August 2024

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Editorial
4.4	Addition of warning on cardiac conduction conditions.
4.5	Addition of drug-drug interaction causing QTc interval prolongation and Torsade de pointes.
4.8	Addition of post-marketing reports for QT interval prolonged, polymorphic ventricular tachycardia including Torsade de Pointes. Update of AE reporting link.
6.5	Addition of: Not all pack sizes may be available.
8	Addition of sponsor email.