

## NEW ZEALAND DATA SHEET – Donepezil IPCA

### 1 PRODUCT NAME

Donepezil IPCA 5mg, 10 mg, film coated tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablets contains 5mg donepezil hydrochloride

Each tablet contains 10 mg donepezil hydrochloride

Excipient(s) with known effect

Contains Lactose

For the full list of excipients, see section 6.1

### 3 PHARMACEUTICAL FORM

Donepezil 10 mg Tablets are yellow colored, circular, biconvex, film coated tablets embossed with 'C' on one side and '6' on the other side.

Donepezil 5 mg Tablets are white to off-white, circular, biconvex, film coated tablets embossed with 'C' on one side and '7' on the other side.

### 4 CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

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

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

#### 4.2 Dose and method of administration

##### *Adults/Elderly*

Treatment should be initiated and supervised by a doctor experienced in the diagnosis and treatment of Alzheimer's Dementia. Individual response to donepezil cannot be predicted. Treatment should be continued for as long as a therapeutic benefit for the patient exists. Discontinuation of therapy should be considered where there is no longer evidence of a therapeutic effect, which should be assessed by periodic evaluations by the physician using input from the patient and caregiver. The use of donepezil in patients with other types of dementia or other types of memory impairment (e.g., age-related cognitive decline), has not been established.

The dosages of donepezil shown to be effective in controlled clinical trials are 5 mg and 10 mg administered once daily. Although there is no statistically significant evidence that a greater treatment effect is obtained from the use of the 10 mg dose, there is a suggestion, based on analysis of group data that some additional benefits may accrue to some patients from the use of the higher dose.

Treatment is initiated at 5 mg/day (once-a-day dosing). Donepezil film-coated tablets should be taken orally, in the evening, just prior to retiring. Donepezil Tablets can be taken with or without food.

The 5 mg/day dose should be maintained for at least one month in order to allow the earliest clinical responses to treatment to be assessed and to allow steady-state concentrations of donepezil to be achieved. Following a one-month clinical assessment of treatment at 5 mg/day, the dose of donepezil 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 is seen. There is no evidence of a rebound effect after abrupt discontinuation of therapy.

### ***Renal & Hepatic Impairment***

A similar dose schedule can be followed for patients with renal or mild to moderate hepatic impairment as clearance of donepezil is not significantly affected by these conditions.

### ***Use in Children***

Donepezil hydrochloride is not recommended for use in children (see Warnings and Precautions - Paediatric Use).

### **4.3 Contraindications**

Donepezil is contraindicated in patients with a known hypersensitivity to donepezil hydrochloride, piperidine derivatives, or to any excipients used in the formulation (see Further Information – List of Excipients).

### **4.4 Special warnings and precautions for use**

#### ***Anaesthesia***

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

#### ***Cardiovascular Conditions***

Because of the 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.

#### ***Gastrointestinal Conditions***

Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory medicines (NSAIDs), should be monitored closely for symptoms of active or occult gastrointestinal bleeding. However, the clinical studies with donepezil at 5 or 10 mg/day showed no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Donepezil, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhoea, nausea and vomiting. These effects, when they occur, appear more frequently with the 10 mg/day dose than the 5 mg/day dose. Although in most cases these effects are mild and transient, sometimes lasting up to three weeks, they have resolved during continued use. Patients should be observed closely at the initiation of treatment and after dose increases.

#### ***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 have the potential to exacerbate or induce extrapyramidal symptoms.

### **Neuroleptic Malignant Syndrome (NMS)**

NMS has been reported to occur very rarely 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.

If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, treatment should be discontinued immediately.

### ***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.

### ***Mortality in Subjects with Vascular Dementia***

Three clinical trials of 6 months duration were conducted studying individuals meeting the NINDS-AIREN criteria for probable or possible vascular dementia (VaD) and excluding patients with a diagnosis of Alzheimer's disease. In the first study, the mortality rates were 2/198 (1.0%) on donepezil 5 mg, 5/206 (2.4%) on donepezil 10 mg and 7/199 (3.5%) on placebo. In the second study, the mortality rates were 4/208 (1.9%) on donepezil 5 mg 3/215 (1.4%) on donepezil 10 mg and 1/193 (0.5%) on placebo. In the third study, the mortality rates were 11/648 (1.7%) on donepezil 5 mg and 0/326 (0%) on placebo ( $p < 0.02$ ). The mortality rate for the three VaD studies combined in the donepezil group (1.7%) was numerically higher than in the placebo group (1.1%); however, this difference was not statistically significant. The majority of deaths in patients taking either donepezil or placebo appear to result from various vascular related causes, which could be expected in this elderly population with underlying vascular disease. An analysis of all serious non-fatal and fatal vascular events showed no difference in the rate of occurrence in the donepezil hydrochloride group relative to placebo.

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

## **4.5 Interaction with other medicines and other forms of interaction**

### ***Drugs Highly Bound to Plasma Proteins***

Drug displacement studies have been performed *in vitro* between this highly bound drug (96%) and other drugs such as frusemide, digoxin, and warfarin. Donepezil at concentrations of 0.3-10  $\mu\text{g/mL}$  did not affect the binding of frusemide (5  $\mu\text{g/mL}$ ), digoxin (2  $\text{ng/mL}$ ) and warfarin (3  $\mu\text{g/mL}$ ) to human albumin. Similarly, the binding of donepezil to human albumin was not affected by frusemide, digoxin and warfarin.

### ***Effect of Donepezil on the Metabolism of Other Drugs***

No *in vivo* clinical trials have investigated the effect of Donepezil on the clearance of drugs metabolised by CYP 3A4 (e.g. cisapride, terfenadine) or by CYP 2D6 (e.g. imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean  $K_i$  about 50- 130  $\mu\text{M}$ ), that, given the therapeutic

plasma concentrations of donepezil (164 nM), indicates little likelihood of interference.

Whether donepezil has any potential for enzyme induction is not known.

Formal pharmacokinetic studies evaluated the potential of donepezil for interaction with theophylline, cimetidine, warfarin and digoxin. No significant effects on the pharmacokinetics of these drugs were observed. Donepezil hydrochloride and/or any of its metabolites does not inhibit the metabolism of thioridazine, risperidone or sertraline in humans.

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

#### **Effect of Other Drugs on the Metabolism of Donepezil**

*In vitro* studies have shown that the cytochrome P450 isoenzymes 3A4 and to a minor extent 2D6 are involved in the metabolism of donepezil. Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro*. Therefore these and other CYP3A4 inhibitors, such as itraconazole and erythromycin, and CYP2D6 inhibitors, such as fluoxetine could inhibit the metabolism of donepezil. Whether there is a clinical effect of these inhibitors is not known. In two studies in healthy volunteers, ketoconazole increased mean donepezil concentrations by about 30%. These increases are smaller than those produced by ketoconazole for other agents sharing the CYP-3A4 pathway and are not likely to be clinically relevant. Administration of donepezil had no effect on the pharmacokinetics of ketoconazole.

Inducers of CYP 2D6 and CYP 3A4 (e.g., phenytoin, carbamazepine, dexamethasone, rifampicin, phenobarbital and alcohol) could increase the rate of elimination of donepezil. Since the magnitude of an inhibiting or inducing effect is unknown, such drug combinations should be used with care.

Formal pharmacokinetic studies demonstrated that the metabolism of Donepezil is not significantly affected by concurrent administration of digoxin, cimetidine, thioridazine, risperidone or sertraline.

Donepezil hydrochloride has the potential to interfere with medications having anticholinergic activity. There is also the potential for synergistic activity with concomitant treatment involving such medications as succinylcholine, other neuro-muscular blocking agents or cholinergic agonists or beta blocking agents which have effects on cardiac conduction, but an *in vitro* study showed that donepezil hydrochloride had minimal effects on hydrolysis of succinylcholine.

#### **4.6 Fertility, pregnancy and lactation**

##### **Fertility**

Donepezil hydrochloride had no effect on fertility in rats up to 10 mg/kg/day (a tissue exposure equivalent to approximately twice that in humans at the maximum recommended clinical dose of 10 mg/day) in male and female rats based on AUC (see Use in Pregnancy and Lactation)

##### **Use in Pregnancy and Lactation**

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 not disclose any evidence for teratogenic potential of donepezil. In rats this dose resulted in a systemic drug exposure in excess of human values. However, in rabbits the extent of systemic drug exposure is not known. Treatment of pregnant rats from late gestation to the end of lactation with an oral donepezil dose of 10 mg/kg/day resulted in a slight increase in incidence of stillborn pups, and slightly reduced pup survival through day 4 postpartum.

There are no adequate or well-controlled studies in pregnant women. Donepezil should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

It is not known whether donepezil hydrochloride is excreted in human breast milk, and there are no studies

in lactating women. Excretion of donepezil and/or its metabolites into milk occurred after oral treatment of nursing rats, with milk concentrations similar to those in plasma. Therefore, women on donepezil should not breast feed.

#### **Paediatric Use**

Donepezil is not recommended for use in children.

#### **4.7 Effects on ability to drive and use machines**

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

#### **4.8 Undesirable effects**

##### *Mild to Moderately Severe Alzheimer's disease Clinical Trials*

Most adverse events are mild in severity and transient in nature. The most common (Incidence  $\geq$  5% and twice the frequency of placebo) were diarrhoea, muscle cramps, fatigue, nausea, vomiting and insomnia. Other common adverse events (incidence  $\geq$  5% and  $\geq$  placebo) were headache, pain, accident, common cold, abdominal disturbance and dizziness. Cases of syncope, bradycardia, sinoatrial block and atrioventricular block were observed. No notable abnormalities in laboratory values associated with treatment were observed except for minor increases in serum concentrations of creatinine kinase. Adverse events observed during long-term but not the short-term trials (incidence  $\geq$  5% and twice the frequency of placebo) included asthenia.

##### *Adverse Events Leading to Discontinuation*

In trials of mild to moderate Alzheimer's disease, the rate of discontinuation for the donepezil 5 mg/day treatment group was comparable to that of placebo-treated patients at approximately 5%. The rate of discontinuation of patients who received rapid dose escalations over 7 days from 5 mg/day to 10 mg/day, was higher at 13%. The most common signs and symptoms leading to discontinuation were nausea, diarrhoea and vomiting. For patients who did not discontinue, these signs and symptoms generally proved to be mild and transient, resolving in 1 to 2 days during continued use of the 10 mg/day dose. There is evidence to suggest that the frequency of these common adverse events may be affected by the rate of titration.

Adverse Events listed below were derived from the 15- and 30-week studies (see Clinical Trials) and a pivotal study of 14 weeks duration.

**Table 1: Adverse events Reported in Controlled Clinical trials in at least 2% of patients receiving Donepezil and at a higher frequency than placebo treated patients**

<b>Haematological and Lymphatic System</b>
Ecchymosis
<b>Metabolic and Nutritional</b>
Weight Decrease
<b>Musculoskeletal System</b>
Muscle Cramps
Arthritis
<b>Nervous System</b>
Insomnia
Dizziness
Depression
Abnormal Dreams
Somnolence
<b>Urogenital</b>
Frequent Urination

### ***Other Adverse Events Observed During Clinical Trials***

Treatment emergent signs and symptoms that occurred during three controlled clinical trials were recorded as adverse events by the clinical investigators using terminology of their own choosing. All adverse events occurring at least twice and judged as possibly or definitely related to donepezil treatment are included, except for those already listed in Table 1. Events are classified by body system and include frequent adverse events - those occurring in at least 1/100 patients; infrequent adverse events - those occurring in 1/100 to 1/1000 patients.

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

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

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

**Metabolic and Nutritional Disorders:** dehydration, oedema of extremities

**Musculoskeletal System:** muscle weakness

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

**Respiratory System:** rhinitis, coughing, dyspnoea

**Skin and Appendages:** rash, abrasion, diaphoresis, pruritus

**Special Senses:** cataract, ear disorder, vision blurred

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

### ***Severe Alzheimer's Disease Clinical Trials***

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

The incidence profile for adverse events for severe Alzheimer's disease was similar to that of mild to moderate Alzheimer's disease.

In controlled clinical trials in severe Alzheimer's disease, the rate of discontinuation due to adverse events was 11.3% in patients treated with donepezil compared to 6.7% in the placebo group. There were no adverse events occurring in at least 2% of patients and twice the incidence seen in placebo patients. Other less common adverse events leading to discontinuation included diarrhoea, nausea, vomiting, urinary tract infection, decreased appetite, and aggression.

The most common adverse events, defined as those occurring at a frequency of at least 5% in patients and twice the placebo rate, were diarrhoea, nausea, and aggression. Overall, the majority of adverse events were judged by the investigators to be mild or moderate in intensity.

### ***Vascular Dementia Clinical Trials***

A comparison of the Alzheimer's disease and vascular dementia studies shows that the types of and relative proportions of adverse events associated with donepezil were similar in the two populations. In the combined vascular dementia studies the mortality rate in the donepezil hydrochloride group (1.7%) was numerically higher than in the placebo group (1.1%) (see Warnings and Precautions – Mortality

in Subjects with Vascular Dementia).

### **Post-marketing Experience**

There have been post-marketing reports of hallucinations, agitation, aggressive behaviour, seizure, abdominal pain, cholecystitis, hepatitis, gastric ulcer, duodenal ulcer, gastrointestinal haemorrhage, heart block, haemolytic anaemia, hyponatraemia, neuroleptic malignant syndrome and pancreatitis. However, there is inadequate data to determine the causal relationship with Interactions.

The administration of donepezil hydrochloride concomitantly with other cholinesterase inhibitors should be avoided.

### **4.9 Overdose**

#### ***Animal Study Data***

The estimated median lethal dose of donepezil hydrochloride following administration of a single oral dose in mice, rats and dogs is 45, 32 and 15 mg/kg, respectively, or approximately 225, 160 and 75 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.

#### ***Cholinergic Crisis***

Over dosage with cholinesterase inhibitors can result in cholinergic crisis characterised 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.

#### ***Treatment***

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

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

As an inhibitor of AChE, donepezil augments cholinergic function in the central nervous system, thereby providing its therapeutic benefit. The enzyme AChE also occurs peripherally in red blood cells, therefore, measurement of AChE activity in erythrocyte membranes provides an index for donepezil pharmacodynamics. This surrogate marker has been evaluated in several human pharmacokinetic/pharmacodynamic trials and in controlled clinical trials.

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

Results from therapeutic drug monitoring showed no apparent relationship between plasma concentration and adverse drug reactions.

It has been demonstrated that Alzheimer's disease is associated with a relative decrease in the activity of the cholinergic system in the cerebral cortex and other areas of the brain. Studies suggest that donepezil hydrochloride exerts its therapeutic effect by enhancing cholinergic function in the central nervous system. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of acetylcholinesterase.

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

### **Alzheimer's Disease**

In patients with Alzheimer's dementia participating in clinical trials, administration of single daily doses of 5 mg or 10 mg of donepezil hydrochloride produced steady-state inhibition of acetylcholinesterase activity (measured in erythrocyte membranes) of 63.6% and 77.3%, respectively when measured post dose. The inhibition of acetyl cholinesterase (AChE) in red blood cells by donepezil hydrochloride 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, AChE inhibition and change in ADAS-cog, a sensitive and well validated scale which examines cognitive performance - including memory, orientation, attention, reason, language and praxis.

### **Clinical trials**

#### ***Mild to Moderately Severe Alzheimer's disease***

##### **Studies of Less than One Year Duration**

The effectiveness of Ipca-Donepezil in the treatment of Alzheimer's disease has been demonstrated by two randomised, double-blind, placebo-controlled studies (15- and 30- week) in which 436 patients were treated with Donepezil hydrochloride. Criteria for inclusion were patients with mild to moderately severe Alzheimer's disease (diagnosed by NINCDS and DSM III-R criteria, Mini- Mental State Examination  $\geq 10$  and  $\leq 26$  and Clinical Dementia Rating of 1 or 2).

**Study Outcome Measures:** In each study, the effectiveness of treatment with donepezil was evaluated using a dual outcome assessment strategy.

The ability of donepezil to improve cognitive performance was assessed with the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), a multi-item instrument that has been extensively validated in longitudinal cohorts of Alzheimer's disease patients. The ADAS-cog examines selected aspects of cognitive performance including elements of memory, orientation, attention, reasoning, language and praxis. The ADAS-cog scoring range is from 0 to 70, with higher scores indicating greater cognitive impairment. Elderly normal adults may score as low as 0 or 1, but it is not unusual for non-demented adults to score slightly higher.

The patients recruited as participants in each study had mean scores on the Alzheimer's Disease Assessment Scale (ADAS-cog) of approximately 26 units, with a range from 4 to 61. Experience gained in longitudinal studies of ambulatory patients with mild to moderate Alzheimer's disease suggest that they gain 6 to 12 units a year on the ADAS-cog.

However, lesser degrees of change are seen in patients with very mild or very advanced disease because the ADAS-cog is not uniformly sensitive to change over the course of the disease. The annualized rate of decline in the placebo patients participating in donepezil trials was approximately 2 to 4 units per year.

The ability of donepezil to produce an overall clinical effect was assessed using a Clinician's Interview Based Impression of Change that required the use of caregiver information, the CIBIC plus. Unlike ADAS-cog, the CIBIC plus is not a single instrument nor is it a standardised instrument like the ADAS-cog. Clinical trials for investigational drugs have used a variety of CIBIC formats, each different in terms of depth and structure. As such, results from a CIBIC plus reflect clinical experience from the trial or trials in which it was used and

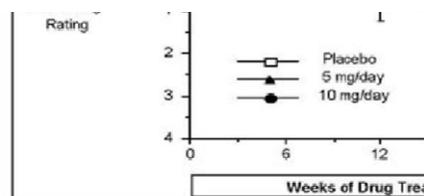
cannot be compared directly with the results of CIBIC plus evaluations from other clinical trials. The CIBIC plus used in donepezil trials was a semi-structured instrument that was intended to examine four major areas of patient function: General, Cognitive, Behavioural and Activities of Daily Living. It represents the assessment of a skilled clinician based upon his/her observations at an interview with the patient, in combination with information supplied by a caregiver familiar with the behaviour of the patient over the interval rated. The CIBIC plus is scored as a seven point categorical rating, ranging from a score of 1, indicating “markedly improved”, to a score of 4, indicating “no change” to a score of 7, indicating “markedly worse”. The CIBIC plus has not been systematically compared directly to assessments not using information from caregivers (CIBIC) or other global methods.

### **Thirty-Week Study**

In a study of 30 weeks duration, 473 patients were randomised to receive single daily doses of placebo, 5 mg/day or 10 mg/day of donepezil. The 30-week study was divided into a 24- week double-blind active treatment phase followed by a 6-week single-blind placebo washout period. The study was designed to compare 5 mg/day or 10 mg/day fixed doses of donepezil to placebo. However, to reduce the likelihood of cholinergic effects, the 10 mg/day treatment was started following an initial 7-day treatment with 5 mg/day doses.

Effects on the ADAS-cog: Figure 1 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 30 weeks of the study. After 24 weeks of treatment; the mean differences in the ADAS-cog change scores for donepezil treated patients compared to the patients on placebo were 2.8 and 3.1 units for the 5 mg/day and 10 mg/day treatments, respectively. These differences were statistically significant. While the treatment effect size may appear to be slightly greater for the 10 mg/day treatment, there was no statistically significant difference between the two active treatments.

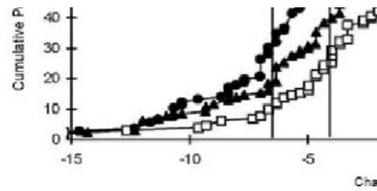
Following 6 weeks of placebo washout, scores on the ADAS-cog for both the donepezil treatment groups were indistinguishable from those patients who had received only placebo for 30 weeks. This suggests that the beneficial effects of donepezil abate over 6 weeks following discontinuation of treatment and do not represent a change in the underlying disease. There is no evidence of a rebound effect 6 weeks after abrupt discontinuation of therapy.



**Figure 1. Time course of the change from Baseline in ADAS-cog score for patients completing 24 weeks of treatment.**

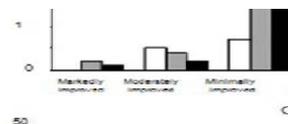
Figure 2 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained the measure of improvement in ADAS-cog score shown on the X axis. Three change scores, (7-point and 4-point reductions from baseline or no change in score) have been identified for illustrative purposes and the percent of patients in each group achieving that result is shown in this inset table.

The curves demonstrate that both patients assigned to placebo and donepezil have a wide range of responses, but that the active treatment groups are more likely to show greater improvements. A curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon or shifted to the right of the curve for placebo, respectively.



**Figure 2:** Cumulative Percentage of patients completing 24 Weeks of double blind treatment with specified changes from Baseline ADAS-cog Scores. The percentages of Randomised patients who completed the study were: Placebo 80%, 5 mg/day 85% and 10 mg/day 68%

Effects on the CIBIC plus: Figure 3 is a histogram of the frequency distribution of CIBIC plus scores attained by patients assigned to each of the three treatment groups who completed 24 weeks of treatment. The mean drug-placebo differences for these groups of patients were 0.35 units and 0.39 units for 5 mg/day and 10 mg/day of donepezil, respectively. These differences were statistically significant. There was no statistically significant difference between the two active treatments.

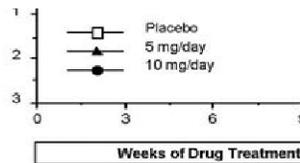


**Figure 3. Frequency Distribution of CI**

### **Fifteen-Week Study**

In a study of 15 weeks duration, patients were randomized to receive single daily doses of placebo or either 5 mg/day or 10 mg/day of donepezil for 12 weeks, followed by a 3-week placebo washout period. As in the 30-week study, to avoid acute cholinergic effects, the 10 mg/day treatment followed an initial 7-day treatment with 5 mg/day doses.

Effects on the ADAS-Cog: Figure 4 illustrates the time course of the change from baseline in ADAS-cog scores for all three dose groups over the 15 weeks of the study. After 12 weeks of treatment, the differences in mean ADAS-cog change scores for the donepezil treated patients compared to the patients on placebo were 2.7 and 3.0 units each, for the 5 and 10 mg/day donepezil treatment groups, respectively. These differences were statistically significant. The effect size for the 10 mg/day group may appear to be slightly larger than that for 5 mg/day. However, the differences between active treatments were not statistically significant.



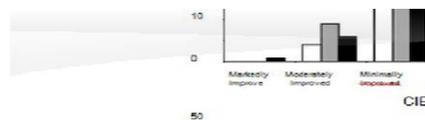
**Figure 4. Time-course of the Change from Completing the**

Following 3 weeks of placebo washout, scores on the ADAS-cog for both the donepezil treatment groups increased, indicating that discontinuation of donepezil resulted in a loss of its treatment effect. The duration of this placebo washout period was not sufficient to characterise the rate of loss of the treatment effect, but the 30-week study (see above) demonstrated that treatment effects associated with the use of donepezil abate within 6 weeks of treatment discontinuation.

Figure 5 illustrates the cumulative percentages of patients from each of the three treatment groups who attained the measure of improvement in ADAS-cog score shown on the X axis. The same three change scores, (7-point and 4-point reductions from baseline or no change in score) as selected for the 30-week study have been used for this illustration. The percentages of patients achieving those results are shown in the inset table.

As observed in the 30-week study, the curves demonstrate that patients assigned to either placebo or to donepezil have a wide range of responses, but that the donepezil treated patients are more likely to show the greater improvements in cognitive performance.

**Effects on the CIBIC plus:** Figure 6 is a histogram of the frequency distribution of CIBIC plus scores attained by patients assigned to each of the three treatment groups who completed 12 weeks of treatment. The differences in mean scores for donepezil treated patients compared to the patients on placebo at Week 12 were 0.36 and 0.38 units for the 5 mg/day and 10 mg/day treatment groups, respectively. These differences were statistically significant.



**Figure 6. Frequency Distribution of**

In both studies, patient age, sex and race were not found to predict the clinical outcome of donepezil treatment

### Studies of Greater Than One Year Duration

The effectiveness of donepezil in the treatment of Alzheimer's disease has been demonstrated by two randomised, double-blind, placebo-controlled studies (54-week) in which 356 patients were treated with donepezil.

### **Fifty Four-Week Study #1**

In a 54-week double-blinded study, patients were randomised to receive either placebo or 5 mg donepezil once daily for 28 days followed by 10 mg once daily for the remainder of the study. Criteria for inclusion included: diagnosis of mild to moderate Alzheimer's disease (DSM-IV, 290.00 or 290.10 of the NINCDS criteria), Clinical Dementia Rating (CDR)=1 or 2, MMSE of 12-20, retention of at least 8 Instrumental Activities of Daily Living (IADLs) and at least 5 basic Activities of Daily Living (ADLs) and a modified Hachinski score  $\leq 4$ . The intent to treat analysis consisted of 207 donepezil-treated patients and 208 placebo patients.

#### **Study outcome measure:**

The primary outcome measure for assessment of efficacy of donepezil was based upon attrition from the study due to clinically evident functional decline. Patients were assessed at 6-week intervals. Attrition was determined by the investigator as follows:

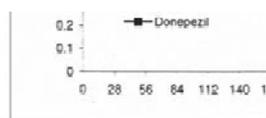
- 1) a clinically significant decline in ability to perform one or more basic ADL which were present at baseline,
- 2) a clinically significant decline in ability to perform 20% or more of IADLs which were present at baseline, or
- 3) an increase in CDR score compared to baseline.

Basic ADL items are defined by the patient's ability in toileting, feeding, dressing, personal hygiene/grooming, bathing and walking. Instrumental ADLs involve the assessment of 10 items: use of telephone, household tasks, using household appliances, managing money, shopping, food preparations, ability to get around inside and outside home, hobbies and leisure activities, handling personal mail, and grasp of situations or explanations. The CDR assesses six cognitive and behavioural domains: memory, orientation, judgement and problem solving, community affairs, home and hobbies and personal care.

#### **Time to attrition:**

In the Kaplan-Meier analysis, donepezil treatment produced significantly greater preservation of function, as determined by time to attrition, than placebo as illustrated in Figure 7 below. By using Log-rank and Wilcoxon tests to compare survival distribution of time to attrition, the median time to attrition was more than 357 days (lower limit of the 95% CI = 280) for donepezil-treated patients, whereas the median time to attrition for placebo treated patients was 208 days (95% CI = [165, 252]). Both Log-rank and Wilcoxon tests indicated that the survival curves for the two treatment groups were significantly different ( $p=0.0019$  and  $p=0.0051$ , respectively).

The hazard ratio (donepezil /placebo) was 0.62 indicating the relative risk of clinically evident function decline for patients who received donepezil was approximately 62% of that of patients who received placebo.



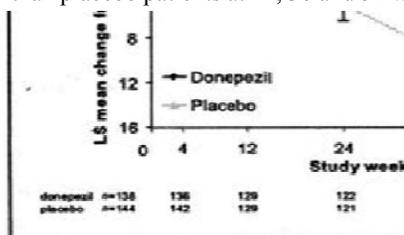
**Figure 7. Estimated Probabilities of Time to Attrition**  
Survival Function Analyses: Intention to Treat

### **Fifty Four-Week Study #2**

In a study of 54 weeks duration, patients were randomised to receive either placebo or 5 mg donepezil once daily, which was increased to 10 mg once daily at day 29 and maintained until the end of the study. Criteria for inclusion included a diagnosis of mild to moderate Alzheimer's disease (DSM-IV, NINCDS-ADRDA criteria and MMSE of 10-26).

Study outcome measure: The primary efficacy variable was the Gottfries, Bråne and Steen (GBS) scale, which assesses global function. It is based on a semi-structured interview with the patient's caregiver. This 27-item scale assesses four domains including intellectual function (12 items), motor function (basic ADLs – 6 items), emotional function (3 items) and behavioural symptoms characteristic for dementia syndromes (6 items).

Global function: On the GBS scale, donepezil-treated patients showed a trend to improvement compared to placebo patients at endpoint analysis (p=0.054). By intention to treat analysis of observed cases, donepezil-treated patients performed significantly better than placebo patients at 24, 36 and 52 weeks.



**Figure 8. LS Mean Change from Baseline for GBS Total Score by Week and Treatment Group - ITT population (Observed Cases and Week 52 LOCF)**

### *Quality of Life*

Although a trend of improvement on quality of life (QOL) measures was observed in clinical trials of donepezil treated patients, there were large variances in QOL scores. These are consistent with observations regarding quality of life assessments in Alzheimer's disease patients generally. It has been demonstrated that Alzheimer's disease patients' opinions will be influenced by the day-to-day fluctuations in their illness (often quite substantial), leading to similar day-to-day variability in their perception of quality of life. Alzheimer's disease patients may also be unreliable sources of information on quality of life because of significant losses in executive functions such as judgement, memory, and insight that are key to obtaining meaningful assessments.

### *Severe Alzheimer's Disease*

The effectiveness of donepezil in the treatment of severe Alzheimer's disease has been demonstrated by three randomised, double-blind, placebo-controlled studies (one 26 week and two 24 week) in which 517 patients were randomised to receive donepezil. Criteria for inclusion were patients with severe Alzheimer's disease (diagnosed by NINCDS-ADRDA and DSM IV criteria, Mini-Mental State Examination (MMSE) and a Functional Assessment Staging (FAST)).

Study Outcome Measures: In each study, the effectiveness of treatment with donepezil was evaluated using a combination of assessments of cognition, global function, activities of daily living (daily function), and behavioural and psychological symptoms.

### ***Cognition***

SIB: The primary tool in the three studies used to assess cognition was the Severe Impairment Battery (SIB). The SIB evaluates cognitive dysfunction over nine domains (social interactions, memory, orientation, language, attention, praxis, visuospatial, construction and orienting to name). Total scores range from 1 to 100, and lower scores indicate greater impairment.

MMSE: Cognitive changes over time are often assessed using the Mini-Mental State Examination (MMSE), a 30 point test. Lower scores indicate a greater degree of impairment, and scores <12 points or <10 points have been used to define the severe stages of dementia. The MMSE was used in 2 of the studies as a secondary endpoint.

### ***Global Function***

CIBIC plus: Similar to the studies in mild to moderate Alzheimer's disease, the Clinician's Interview Based Impression of Change with caregiver input (CIBIC plus) was used as a primary endpoint to assess global function for two of the three studies.

CGI-I: In one of the studies, the Clinical Global Impression of Improvement (CGI-I) was used as a primary endpoint as a measure of global function. Similar to CIBIC plus, the physician rates the patient's condition relative to baseline on a 7-point Likert-like scale, with of 1-3 representing degrees of improvement, 4 representing no change, and 5-7 representing degrees of worsening.

### ***Activities of Daily Living***

ADCS-ADL-severe: To assess activities of daily living (ADL), all three studies used the modified ADCS-ADL inventory for severe Alzheimer's disease (ADCS-ADL-severe). This is based on an interview with the caregiver and measures the patient's most usual and consistent ability to perform basic and instrumental ADL during the previous 4 weeks. The scale ranges from 0 to 54, with lower scores indicating greater functional impairment.

### ***Behavioural and Psychological Symptoms***

Two scales were used to assess behavioural and psychological symptoms: the neuropsychiatric inventory (NPI) and the Behavioural Pathology in Alzheimer's disease scale (BEHAVE-AD).

NPI: The 12 item NPI, used in 2 studies, is based on the caregiver's assessment of the frequency and severity of a range of mood and behavioural disturbances since the last evaluation. Total NPI scores range from 0 (best score) to 144 (worst score).

BEHAVE-AD: The BEHAVE-AD scale, used in 1 study, is similarly based on the caregiver's assessment of the presence and magnitude of a range of neuropsychiatric symptoms over the past two weeks. Total BEHAVE-AD scores range from 0 (best score) to 78 (worst score).

### **Twenty-Six-Week Study**

In a study of 26 weeks duration, safety and efficacy were evaluated by randomizing 249 patients to receive a single daily dose of placebo or 10 mg/day of donepezil. To reduce the likelihood of cholinergic effects, treatment was initiated at 5 mg/day for 4 weeks, then treatment was increased to 10 mg/day, based on clinical judgement. At any time during the study, the dose of donepezil could be reduced from 10 mg to 5 mg daily based on the investigator's assessment of tolerability. The primary endpoints for this study were the effects on the SIB and the ADCS-ADL-severe scores.

Effect on the SIB: Figure 9 illustrates the time course of the change in baseline in the SIB. After 26 weeks of treatment, the mean difference in the SIB change scores for donepezil- treated patients compared to patients on placebo was 5.7 points. The difference was statistically significant ( $p=0.008$ ).



**Figure 9. Time-course of the Change from Baseline in SIB score for Patients Completing 26 Weeks of Treatment.**

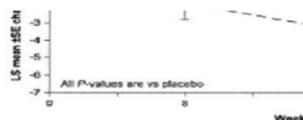
Effect on the ADCS-ADL-severe Score: After 26 weeks of treatment, the donepezil- treated patients showed significantly less decline (-1.4 points) than the patients on placebo (- 3.0 points) (p=0.029).

In this study CGI-I, MMSE and NPI were used as secondary endpoints. The percentage of patients showing any degree of improvement in the CGI-I was 53.2% for donepezil-treated patients and 38.3% in the placebo, while the distribution for patients in the worsened category was greater for the placebo treated-patients (25.2% placebo versus 20.7% donepezil-treated). The differences were statistically significant (p=0.0395). Donepezil treated patients showed a significantly greater mean improvement (1.5 points) than placebo- treated patients (0.1 points) in the MMSE score (p=0.009). There was no statistically significant difference between the treatment groups for the NPI.

**Twenty-Four-Week Study #1**

In a study of 24 weeks duration, 343 patients were randomised to receive single daily doses of placebo or 10 mg/day of donepezil. Patients received 5 mg for the first six weeks of the study and then 10 mg for the remainder of the double-blind period. At any time during the study, the dose of donepezil could be reduced from 10 mg to 5 mg daily based on the investigator's assessment of tolerability. The primary endpoints for this study were the effects on the SIB and the CIBIC plus scores.

Effect on the SIB: Figure 10 illustrates the time course of the change in baseline in the SIB. After 24 weeks of treatment, the mean difference in the SIB change scores for donepezil-treated patients compared to patients on placebo was 5.3 points. The difference was statistically significant (p=0.0001).



**Figure 10. Time-course of the Change from Baseline in SIB score for Patients Completing 24 Weeks of Treatment.**

Effect on the CIBIC plus Score: The percentage of patients showing any degree of improvement was 27.8% for donepezil-treated patients and 22.7% for the placebo group. This was statistically significant (p=0.0473).

For the other outcome measures donepezil-treated patients showed a significantly greater mean improvement (0.7 points) than placebo-treated patients (0.0 points) in the MMSE score (p=0.0267). There were no statistically significant differences between the treatment groups for the ADCS-ADL-severe or NPI scales.

Long term efficacy data are provided by an open label extension of this study. After 36 weeks of donepezil treatment, the mean SIB value remained at or near the baseline level, suggesting no further decline in cognitive functions.

In a study of 24 weeks duration, 325 patients were randomised to receive single daily doses of placebo, low dose donepezil or high dose donepezil. For the low dose 3 mg/daily (dosage only used in Japan) was administered for the first 2 weeks, then this was increased to 5 mg/day. For the high dose group, 3 mg/day was administered for the first 2 weeks, then 5 mg/day was administered for 4 weeks, and from week 6 onwards, 10 mg/day was administered.

Patients assigned to the 10 mg group needed to be able to tolerate the 10 mg/day dose to continue with the study. Patients who could not tolerate this dose were discontinued from the study. The primary endpoints used were the SIB score and the CIBIC- plus score.

Effect on the SIB: After 24 weeks of treatment, the donepezil-treated patients showed a mean improvement (6.7 points in the 5 mg group and 8.9 points in the 10 mg group) compared to the patients on placebo. At both dose levels the difference was statistically significant ( $p < 0.0001$ ).

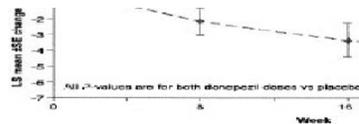


Figure 11. Time-course of the Change for Patients Completing 24 Weeks

**Effect on global function:** The percentage of patients showing any degree of improvement was 46.7% in the group treated with 10 mg of donepezil, 32.3% for the 5 mg donepezil-treated group and 23.8% for placebo treated-patients. The difference was significantly different for the 10 mg group ( $p = 0.001$ ), but not for the 5 mg group ( $p = 0.129$ ).

There were no statistically significant differences between the treatment groups for the ADCS-ADL-severe and BEHAVE-AD scales.

In the three studies, SIB scores, CIBIC plus/CGI-I scores and ADCS-ADL-severe scores were not influenced by age, gender or by the diagnosis of probable versus possible Alzheimer's disease.

### Vascular Dementia

Efficacy of treatment of vascular dementia with donepezil has been investigated in two placebo-controlled trials of 6-months duration in which the diagnostic criteria for vascular dementia proposed by the NINDS-AIREN consensus group (National Institute of Neurological Disorders and Stroke – *Association Internationale pour la Recherche et l'Enseignement en Neurosciences*) were used to define the population of patients studied.

An overall analysis was done at the conclusion of donepezil treatment using a combination of three efficacy criteria. Patients who fulfilled the criteria listed below were considered treatment responders. Response was defined as (1) improvement of ADAS-Cog of at least 4 points; and (2) improvement or no deterioration of CIBIC+; and (3) improvement or no deterioration of Clinical Dementia Rating functionality subscale.

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

Donepezil 5 mg Group	21%
Donepezil 10 mg Group	25%

#p=0.052; \*p<0.05; \*\*p<0.01

## 5.2 Pharmacokinetics properties

### Absorption

Donepezil is well absorbed with a relative oral bioavailability of 100% and reaches peak plasma concentrations in 3 to 4 hours. Oral administration of donepezil produces highly predictable plasma concentrations where 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.

Neither food nor time of administration (morning versus evening dose) affect the absorption of donepezil hydrochloride.

### Distribution

The steady state volume of distribution is 12 L/kg. Donepezil hydrochloride is approximately 96 % bound to human plasma proteins. The distribution of donepezil 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 <sup>14</sup>C-labeled donepezil hydrochloride, approximately 28% of the label remained unrecovered. This suggests that donepezil and/or its metabolites may persist in the body for more than 10 days. The average CSF: plasma ratio for both doses, expressed as a percent of the concentration in plasma, was 15.7%.

### Metabolism/Excretion

Donepezil is both excreted in the urine intact and extensively metabolized to four major metabolites, two of which are known to be active, and a number of minor metabolites, not all of which have been identified. Three of the human metabolites of donepezil have not undergone extensive safety tests in animals. These comprise two O-demethylated derivatives and an N-oxidation product. Donepezil is metabolised by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation. The rate of metabolism of donepezil is slow and does not appear to be saturable. These findings are consistent with the results from formal pharmacokinetic studies which showed that donepezil and/or its metabolites does not inhibit the metabolism of theophylline, warfarin, cimetidine, or digoxin in humans. Pharmacokinetic studies also demonstrated that the metabolism of donepezil is not affected by concurrent administration of digoxin or cimetidine (See Interactions).

Following administration of <sup>14</sup>C-labeled donepezil, plasma radioactivity, expressed as a percent of the administered dose, 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. Approximately 57% of the total radioactivity was recovered in urine and faeces, respectively, over a period of 10 days, while 28% remained unrecovered, with about 17% of the donepezil dose recovered in the urine as unchanged drug. There is no evidence to suggest enterohepatic recirculation of donepezil 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.

### **5.3 Preclinical Safety Data**

#### **Mutagenicity**

Donepezil hydrochloride was not mutagenic in bacterial or in the mouse lymphoma forward mutation assay *in vitro*. Donepezil did not induce unscheduled DNA synthesis in rat primary hepatocyte cultures following oral dosing of the animals. In the chromosome aberration test in cultures of Chinese hamster lung cells, some clastogenic effects were observed in the *in-vivo* mouse micronucleus model.

#### **Carcinogenicity**

No evidence of carcinogenicity was found in long-term studies in mice and rats with dietary dosing of donepezil resulting in peak plasma concentrations of up to 17 times and 6-19 times, respectively, that in humans at the recommended clinical dose of 10 mg/day.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Donepezil tablets also contain the excipients: Lactose, microcrystalline cellulose dried Maize starch, hydroxy propyl cellulose, sodium stearyl fumarate, hypromellose titanium dioxide, purified talc, Macrogol 6000, ferric oxide yellow (For 10 mg), Purified Water

### **6.2 Incompatibilities**

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

### **6.3 Shelf life**

36 months

### **6.4 Special precautions for storage**

Donepezil Tablets should be stored at a temperature at or below 30°C in the original container.

### **6.5 Nature and contents of container**

Donepezil Tablets are available in blisters of 10 and 14\* tablets. These are placed in an outer carton to give a pack size of 84 and 90 tablets.

\*Not all pack sizes are marketed.

### **6.6 Special precautions for disposal**

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

## **7 MEDICINE SCHEDULE**

Prescription Medicine.

## **8 SPONSOR**

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Distributed by : Miro Healthcare Ltd.,  
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**9 DATE OF FIRST APPROVAL**

22.05.2014

**10 DATE OF REVISION OF THE TEXT**

28.07.2023

**SUMMARY TABLE OF CHANGES**

Section changed	Summary of new information
28.02.2023, 8	Product name and sponsor change
1.	Product name change
Throughout	In-line with medsafe datasheet template
6.5	Additional pack size 84
8	Sponsor details updated
6.3	Shelf life updation

