1. NAME OF THE MEDICINAL PRODUCT

Donepezil Mevon 5 mg film-coated tablets
Donepezil Mevon 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5mg of donepezil hydrochloride equivalent to 4.56 mg of donepezil in free base form.

Excipients:
91.25 mg lactose for each film-coated tablet. For the complete list of excipients, see section 6.1.

Each tablet contains 10mg of donepezil hydrochloride equivalent to 9.12 mg of donepezil in free base form.

Excipients:
182.50 mg lactose for each film-coated tablet. For the complete list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Donepezil Mevon 5mg film-coated tablets are white, round, biconvex film-coated tablets.

Donepezil Mevon 10mg film-coated tablets are yellow, round, biconvex film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Donepezil Mevon tablets are indicated for the symptomatic treatment of mild to moderate and severe Alzheimer’s dementia.

4.2 Posology and method of administration

Adults/Elderly
The treatment begins with 5mg/day (single daily dose). The 5mg/day dose must be kept for at least one month so that the initial response to the treatment may be assessed and the donepezil hydrochloride concentrations in the equilibrium state may be achieved. After 4-6 weeks clinical assessment of the 5mg/day one-month treatment, the dosage of Donepezil may be increased to 10mg/day (single daily dose).

After discontinuation of the treatment, a gradual reduction in the beneficial effects of Donepezil is observed. There is no evidence of a rebound effect after abrupt discontinuation of therapy.

Hepatic and renal failure
A similar posology may be adopted for patients with renal failure, since clearance of donepezil hydrochloride is not affected by this condition.

Due to the possible exposition increase in patients suffering from mild to moderate hepatic failure (see section 5.2), dose escalation must be prescribed according to the tolerability of individual patients. There is no information available for patients with severe hepatic failure.

Children:
The use of Donepezil is not recommended for children.

4.3 Contraindications

Donepezil is contraindicated in patients with known hypersensitivity to donepezil hydrochloride, piperidine derivatives, or to any of the excipients used in the formula. Donepezil is contraindicated in pregnancy.

4.4 Special warnings and precautions for use

The use of Donepezil in patients with severe Alzheimer's disease, any other forms of dementia, or other types of changes in memory (e.g. age related cognitive decline) was not assessed. The treatment must be started and monitored by a doctor experienced in the diagnosis and treatment of dementia of the Alzheimer type. The diagnosis must be performed according to the accepted guidelines (for example, DSM IV, ICD 10). Donepezil therapy must only begin if there is a healthcare provider available to regularly monitor the taking of the medicine by the patient. The maintenance treatment may continue as long as the therapeutic benefit for the patient is maintained. Therefore, the clinical benefit of donepezil must be regularly reassessed. When there is evidence that the therapeutic effect no longer exists, discontinuation must be considered. Individual responses to donepezil cannot be foreseen.

Anaesthesia: Donepezil, as a cholinesterase inhibitor, may potentiate muscular relaxing of the succinilcoline type, during anaesthesia.

Cardiovascular Diseases: Due to their pharmacological action, cholinesterase inhibitors may have vagotonic effects on the cardiac rhythm (e.g. bradycardia). This effect may manifest as bradycardia or heart block in patients both with and without known underlying cardiac conduction abnormalities.

There have been post marketing reports of QTc interval prolongation and Torsades de Pointes. Caution is advised in patients with pre-existing or family history of QTc prolongation, in patients treated with drugs affecting the QTc interval, or in patients with relevant pre-existing cardiac disease (e.g., uncompensated heart failure, recent myocardial infarction, bradyarrhythmias), or electrolyte disturbances (hypokalaemia, hypomagnesaemia). Clinical monitoring (ECG) may be required.

Peptic Ulcer Disease and GI Bleeding: Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult, gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent non-steroidal anti-inflammatory drugs (NSAIDS). Results of a controlled clinical study showed that donepezil hydrochloride 10 mg/day, caused peptic ulcer disease (0.2%) and gastrointestinal bleeding from any site (0.6%).

Genitourinary tract: Although this was not observed in the clinical trials with Donepezil, cholinomimetics may cause symptoms of urinary obstruction.

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

Neurological diseases: Convulsions: cholinomimetics are believed to have some potential to cause generalized convulsions. However, convulsions may themselves be a manifestation of Alzheimer's Disease.

Weight Loss: Weight loss was reported as an adverse event, in 2.5% of patients assigned to 10 mg donepezil hydrochloride. Compared to their baseline weights, 4.9% of the group taking 10 mg donepezil hydrochloride were found to have a weight loss of $\geqslant$ 7% at the end of the study.

Cholinomimetics may have the capacity to exacerbate or induce extrapyramidal symptoms.

Pulmonary diseases: Due to their cholinomimetic action, cholinesterase inhibitors should be prescribed with caution to patients with a history of asthma or obstructive pulmonary disease.

The administration of Donepezil concomitantly with other acetylcholinesterase inhibitors, agonists or antagonists of the cholinergic system should be avoided.

Severe hepatic failure: There is no information available for patients with severe hepatic failure.

This medicinal product contains lactose. Patients with severe congenital lactose intolerance, lactase deficiency or glucose galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Donepezil hydrochloride and/or any of its metabolites do not inhibit the metabolism of theophylline, warfarin, cimetidine or digoxin in humans. The metabolism of donepezil hydrochloride is not affected by concurrent administration of digoxin or cimetidine. In vitro studies have shown that the cytochrome P450 isoenzymes 3A4 and to a minor extent 2D6 are involved in the metabolism of donepezil. 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.

Cases of QTc interval prolongation and Torsades de Pointes have been reported for donepezil. Caution is advised when donepezil is used in combination with other medicinal products known to prolong the QTc interval and clinical monitoring (ECG) may be required. Examples include:

- Class IA antiarrhythmics (e.g., quinidine)
- Class III antiarrhythmics (e.g., amiodarone, sotalol)

- Certain antidepressants (e.g., citalopram, escitalopram, amitriptyline)
- Other antipsychotics (e.g., phenothiazine derivatives, sertindole, pimozide, ziprasidone)
- Certain antibiotics (e.g., clarithromycin, erythromycin, levofloxacin, moxifloxacin)

4.6 Pregnancy and lactation

Pregnancy:
There are no adequate data from the use of donepezil in pregnant women. Studies in animals have not shown teratogenic effect but have shown peri and post natal toxicity (see Section 5.3 preclinical safety data). The potential risk for humans is unknown. Donepezil should not be used during pregnancy unless clearly necessary.

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

4.7 Effects on the ability to drive and use machines

Dementia may affect the ability to drive or use machines. Moreover, donepezil may induce fatigue, dizziness and muscle cramps mainly when initiating or increasing the dose. The ability of the patients treated with donepezil to continue driving or using complex machines must be routinely assessed by the responsible doctor.

4.8 Undesirable effects

The most common adverse events are diarrhoea, muscle cramps, fatigue, nausea, vomiting and insomnia.
The incidence profile for adverse events for severe Alzheimer's disease is similar to that of mild to moderately severe Alzheimer's disease.
Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10) common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, <1/100), rare (≥1/10,000, <1/1,000); very rare (< 1/10,000) and not known (cannot be estimated from available data).

System Organ Class	Very Common	Common	Uncommon	Rare	Frequency Unknown
Infections and infestations		Common cold			
Metabolism and nutrition disorders		Anorexia			
Psychiatric disorders		Hallucinations** Agitation** Aggressive behavior**			
Nervous system disorders		Syncope* Dizziness Insomnia	Seizure*	Extrapyramidal symptoms	

Cardiac disorders			Bradycardia	Sino-atrial block Atrioventricular block	Polymorphic ventricular tachycardia including Torsades de Pointes; Electrocardiogram QT interval prolonged
Gastrointestinal disorders	Diarrhea Nausea	Vomiting Abdominal disturbance	Gastrointestinal haemorrhage Gastric and duodenal ulcers		
Hepato-biliary disorders				Liver dysfunction including hepatitis***	
Skin and subcutaneous tissue disorders		Rash Pruritus			
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		Accidents including falls			

*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 fatal dose of donepezil hydrochloride after administering a single oral dose in mice and rats is 45 and 32mg/kg, respectively, or approximately 225 and 160 times the maximum 10 mg daily dose recommended for human beings. Signs of cholinergic stimulation related with the dose were observed in animals, including the reduction of spontaneous movements, prone position, unsteady walk, lacrimation, clonic convulsions, respiratory depression, fasciculation and lower body surface temperature.
Overdose with cholinesterase inhibitors may provoke cholinergic crisis characterized by accentuated nausea, vomiting, salivation, sudation, bradycardia, hypotension, respiratory depression, collapse and convulsions. An increase in muscle weakness might occur, which may be fatal if respiratory muscles are involved.
As in any case of overdose, general support measures must be used. Tertiary anticholinergics, such as atropine, can be used as antidotes in Donepezil overdose. The intravenous administration of atropine sulphate, dosed for the effect, is recommended: initial dose of 1.0 to 2.0 mg IV and subsequent doses based on the clinical response. Uncommon responses in blood pressure and cardiac rhythm have been reported with other cholinomimetics, when administered concomitantly with other quarternary anticholinergics, such as glycopyrrolate. It is unknown whether donepezil

hydrochloride and/or its metabolites may be eliminated by dialysis (haemodialysis, 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 1,000 times more potent an inhibitor of this enzyme than of butyrylcholinesterase, an enzyme which is present mainly outside the central nervous system.

Mild to Moderately Severe 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 produced steady-state inhibition of acetylcholinesterase activity (measured in erythrocyte membranes) of 63.6% and 77.3%, respectively when measured post dose. The inhibition of acetylcholinesterase (AChE) in red blood cells by donepezil hydrochloride has been shown to correlate to changes in ADAS-cog, a sensitive scale which examines selected aspects of cognition. The potential for donepezil hydrochloride to alter the course of the underlying neuropathology has not been studied. Thus Donepezil hydrochloride cannot be considered to have any effect on the progress of the disease.

Efficacy of treatment of Alzheimer's dementia with Donepezil has been investigated in four placebo-controlled trials, 2 trials of 6-month duration and 2 trials of 1-year duration.

In the 6 months clinical trial, an analysis was done at the conclusion of donepezil treatment using a combination of three efficacy criteria: the ADAS-Cog (a measure of cognitive performance), the Clinician Interview Based Impression of Change with Caregiver Input (a measure of global function) and the Activities of Daily Living Subscale of the Clinical Dementia Rating Scale (a measure of capabilities in community affairs, home and hobbies and personal care).
Patients who fulfilled the criteria listed below were considered treatment responders.

Response = Improvement of ADAS-Cog of at least 4 points
No deterioration of CIBIC
No deterioration of Activities of Daily Living Subscale
of the Clinical Dementia Rating Scale

	% Response	
	Intent to Treat Population n=365	Evaluable Population n=352
Placebo Group	10%	10%
Donepezil 5-mg Group	18%*	18%*
Donepezil 10-mg Group	21%*	22%**

*$p<0.05$
** $p<0.01$
Donepezil produced a dose-dependent statistically significant increase in the percentage of patients who were judged treatment responders.

Severe Alzheimer's disease
Efficacy of treatment with Donepezil in severe Alzheimer's disease has been investigated in three placebo-controlled trials of 6-month duration.

In each of the clinical trials, an analysis was done at the conclusion of donepezil treatment using a combination of three efficacy criteria: the total Severe Impairment Battery (SIB - a measure of cognitive performance in all three trials) score, the Clinician's Interview Based Impression of Change with caregiver input (CIBIC+ - a measure of global function in two trials) or Clinical Global Impression of Change (CGI-I - a measure of global function in one trial) and the modified Alzheimer's Disease Cooperative Study - Activities of Daily Living inventory for severe Alzheimer's disease (ADCS-ADL-sev - a measure of function in all three trials).
Patients who fulfilled the criteria listed below were considered treatment responders.

Response = Improvement of SIB of at least 4 points
No deterioration of CIBIC+ or CGI-I
No deterioration of ADCS-ADL-sev

	% Response	
	Intent to Treat Population n=571	Evaluable Population n=518
Placebo Group	10%	10%
ARICEPT 10-mg Group	29%**	30%**

** $p<0.001$

5.2 Pharmacokinetic properties

Absorption: Maximum plasma levels are reached approximately 3 to 4 hours after oral administration. Plasma concentrations and area under the curve rise in proportion to the dose. The terminal disposition half-life is approximately 70 hours, thus, administration of multiple single-daily doses results in gradual approach to steady-state. Approximate steady-state is achieved within 3 weeks after initiation of therapy. Once at steady-state, plasma donepezil hydrochloride concentrations and the related pharmacodynamic activity show little variability over the course of the day.
Food did not affect the absorption of donepezil hydrochloride.

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

Metabolism/Excretion: Donepezil hydrochloride is both excreted in the urine intact and metabolised by the cytochrome P450 system to multiple metabolites, not all of which have been identified. Following administration of a single 5 mg dose of ^{14}C-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 3,000 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 INFORMATION

6.1 Excipients list

Nucleus:
Lactose monohydrate
Microcrystalline Cellulose
Hydroxypropylcellulose
Magnesium Stearate
Maize Starch

Coating:
Talc
PEG 400
Hydroxypropyl methyl cellulose
Titanium dioxide (E171)
Yellow iron oxide (only for Donepezil Mevon 10mg film-coated tablets)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

24 months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Donepezil film coated tablets are supplied in packages of 7, 28, 56 and 60 tablets coated by a film, packaged in transparent blister of PVC+PVdC/Aluminium

It is possible that some of the presentations included are not marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE MARKETING AUTHORISATION

Novem Healthcare Pte Ltd
23 New Industrial Road
#03-08 Solstice Business Center
Singapore 536209

8. DATE OF TEXT REVISION

October 2022