ข้อความบนเอกสารกำกับยา
ข้อความเหมือนกันทุกขนาดบรรจุ
เอกสารกำกับยาภาษาอังกฤษ
TONIZEP FDT 5, 10

1. PRODUCT NAME

TONIZEP FDT 5

TONIZEP FDT 10

2. NAME AND STRENGTH OF ACTIVE INGREDIENT

TONIZEP FDT 5: 5 mg donepezil hydrochloride tablets each containing 4.56 mg donepezil free base.

TONIZEP FDT 10: 10 mg donepezil hydrochloride tablets each containing 9.12 mg donepezil free base

3. PRODUCT DESCRIPTION

Orodispersible tablets.

TONIZEP FDT 5: white round tablet with the figure “5” on one side and the letter “ZD” on the other side.

TONIZEP FDT 10: yellow, round tablet embossed with “10” on one side and “ZD” on another side.

4. PHARMACODYNAMICS/PHARMACOKINETICS

4.1 Pharmacodynamics [1-11], [3-19]

The pharmacotherapeutic group: drugs for dementia; ATC-code N06DA02.

Donepezil hydrochloride is a specific inhibitor of acetylcholinesterase, the predominant cholinesterase in the brain. The drug binds reversibly with and inactivates cholinesterase, thus inhibiting hydrolysis of acetylcholine. As a result, the concentration of acetylcholine increases at cholinergic synapses. Donepezil hydrochloride is *in vitro* over 1000 times more potent an inhibitor of this enzyme than of butyrylcholinesterase, an enzyme which is present mainly outside the central nervous system.

[1-11] เอกสารอ้างอิง 1 : AHFS Drug Information 2012 หน้า 1266 หมายเลข 11

[3-19] เอกสารอ้างอิง 3 : เอกสารกำกับยาต้นแบบที่ได้รับอนุมัติจากอย. หมายเลข 19

Alzheimer's dementia [3-20]

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 hydrochloride produced steady-state inhibition of acetylcholinesterase activity (measured in erythrocyte membrane) 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 hydrochloride has been investigated in four placebo-controlled trials, 2 trials of 6-month duration and 2 trials of 1-year duration.

In the 6-month clinical trial, an analysis was done at the conclusion of donepezil hydrochloride treatment using a combination of three efficacy criteria: the ADAS-cog (a measure of cognitive performance), the Clinician's Interview Based Impression of Change with caregiver input (CIBIC+ - 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 hydrochloride 5-mg group	18%*	18%*
Donepezil hydrochloride 10-mg group	21%*	22%**

* $p < 0.05$

** $p < 0.01$

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

Severe Alzheimer's disease

Efficacy of treatment with donepezil hydrochloride 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 hydrochloride 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 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%
Donepezil hydrochloride 10-mg group	29%**	30%**

** $p < 0.001$

Vascular dementia [3-21]

Efficacy of treatment of vascular dementia with donepezil hydrochloride has been investigated in three placebo-controlled trials of 6-month 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 hydrochloride treatment using a combination of three efficacy criteria.

Patients who fulfilled the criteria listed below were considered treatment responders.

Response = Improvement of ADAS-cog of at least 4 points *and*
Improvement or no deterioration of CIBIC+ *and*
Improvement or no deterioration of Clinical Dementia Rating functionality subscale

	% Response	
	Intent to Treat Population n = 1176	Observed Cases n = 955
Placebo group	16%	16%
Donepezil hydrochloride 5-mg group	21%*	22%[#]
Donepezil hydrochloride 10-mg group	25%**	27%**

\# p = 0.052

* p < 0.05

** p < 0.01

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

[3-20]- [3-21] เอกสารอ้างอิง 3 : เอกสารกำกับยาต้นแบบที่ได้รับอนุมัติจากอย. หมายเลข 20 และ 21 ตามลำดับ

4.2 Pharmacokinetics

Absorption [3-22]: Donepezil hydrochloride is well absorbed [4-2] and food does not affect the absorption of the drug. 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 pharmacodynamics activity show little variability over the course of the day.

Distribution [3-23]: Donepezil hydrochloride is approximately 96% bound to human plasma proteins (to albumin approximately 75% and α_1-acid glycoprotein approximately 21%). [2-2] The plasma protein binding of the active metabolite 6-O-desmethyl donepezil is not known. The steady-state volume of distribution is 12 to 16 L/kg. [2-1] 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 [3-24]: Donepezil hydrochloride is metabolized by the cytochrome P450 (CYP-450) isoenzymes 2D6 and 3A4 to multiple metabolites, [2-3] 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 feces, suggesting biotransformation and urinary excretion as the primary routes of elimination. There is no evidence to suggest enterohepatic recirculation of donepezil hydrochloride and/or any of its metabolites.

Plasma donepezil hydrochloride concentrations decline with a half-life of approximately 70 hours and the mean apparent plasma clearance is 0.13 to 0.19 L/h/kg. [2-4]

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

has not been formally studied in healthy elderly subjects, or in Alzheimer's or vascular dementia patients. However, mean plasma levels in patients closely agreed with those of young healthy volunteers.

Patients with mild to moderate hepatic impairment had increased donepezil hydrochloride steady-state concentrations; mean AUC by 48% and mean C_{max} by 39% (see section 6).

[2-1]- [2-4] เอกสารอ้างอิง 2 : Drug Facts and Comparison 2012 หน้า 1681 หมายเลข 1-4
[3-22]- [3-24] เอกสารอ้างอิง 3 : เอกสารกำกับยาต้นแบบที่ได้รับอนุมัติจากอย. หมายเลข 22-24
[4-2] เอกสารอ้างอิง 4 : Drug Information Handbook with international trade names index 2010-2011, 19th edition หน้า 521 หมายเลข 2

5. INDICATION [3-1]

TONIZEP FDT tablets are indicated for the symptomatic treatment of:

- Mild, moderate and severe Alzheimer's disease.
- Vascular dementia (dementia associated with cerebrovascular disease).

[3-1] เอกสารอ้างอิง 3 : เอกสารกำกับยาต้นแบบที่ได้รับอนุมัติจากอย. หมายเลข 1

6. RECOMMENDED DOSE [3-2]

Adults/Elderly: [1-9]

Treatment is initiated at 5 mg/day (once-a-day dosing). The 5 mg/day dose should be maintained for at least one month in order to allow steady-state concentrations of donepezil hydrochloride to be achieved. Following a 4-6 weeks of clinical assessment in patients who tolerated treatment at 5 mg/day, the dose of TONIZEP FDT can be increased to 10 mg/day (once-a-day dosing). The maximum recommended daily dose is 10 mg. Doses greater than 10 mg/day have not been studied in clinical trials.

Upon discontinuation of treatment, a gradual abatement of the beneficial effects of TONIZEP FDT is seen. There is no evidence of a rebound effect after abrupt discontinuation of therapy.

Renal and hepatic impairment: [1-10]

A similar dose schedule can be followed for patients with impairment as clearance of donepezil hydrochloride is not affected by this condition.

Due to possible increased exposure in mild to moderate hepatic impairment (see section 4.2), dose escalation should be performed according to individual tolerability. There are no data for patients with severe hepatic impairment.

Children:

TONIZEP FDT is not recommended for use in children.

[1-9]- [1-10] เอกสารอ้างอิง 1 : AHFS Drug Information 2012 หน้า 1265 หมายเลข 9-10

[3-2] เอกสารอ้างอิง 3 : เอกสารกำกับยาต้นแบบที่ได้รับอนุมัติจากอย. หมายเลข 2

7. MODE OF ADMINISTRATION [1-1], [3-3]

TONIZEP FDT should be taken orally, in the evening, just prior to retiring. The tablet should be placed on the tongue and allowed to disintegrate before swallowing with or without water, according to patient preference.

[1-1] เอกสารอ้างอิง 1 : AHFS Drug Information 2012 หน้า 1266 หมายเลข 1

[3-3] เอกสารอ้างอิง 3 : เอกสารกำกับยาต้นแบบที่ได้รับอนุมัติจากอย. หมายเลข 3

8. CONTRAINDICATION

TONIZEP FDT is contraindicated in patients with a known hypersensitivity to donepezil hydrochloride, piperidine derivatives, or to any excipients used in the formulation. [1-2], [3-4], [2-5]

TONIZEP FDT is contraindicated in pregnancy. [3-4]

[1-2] เอกสารอ้างอิง 1 :AHFS Drug Information 2012 หน้า 1265 หมายเลข 2

[2-5] เอกสารอ้างอิง 2 :Drug Facts and Comparison 2012 หน้า 1681 หมายเลข 5

[3-4] เอกสารอ้างอิง 3 : เอกสารกำกับยาต้นแบบที่ได้รับอนุมัติจากอย. หมายเลข 4

9. WARNINGS AND PRECAUTIONS

Treatment should be initiated by a physician experienced in the treatment of dementia. Diagnosis should be made according to accepted guidelines (e.g. DSM IV, ICD 10). Therapy with donepezil hydrochloride should only be started if a caregiver is available who will regularly monitor drug intake for the patient. Maintenance treatment can be continued for as long as a therapeutic benefit for the patient exists. Therefore, the clinical benefit of donepezil hydrochloride should be reassessed on a regular basis. Discontinuation should be considered when evidence of a therapeutic effect is no longer present. Individual response to donepezil hydrochloride cannot be predicted. The use of donepezil hydrochloride in patients with other types of dementia or other types of memory impairment (e.g. amnestic mild cognitive impairment), is under investigation. [3-5]

Anaesthesia [1-3], [3-6]*:* Donepezil hydrochloride, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia.

Cardiovascular conditions [1-5], [2-6], [3-7]*:* Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate (e.g. bradycardia). The potential for this action may be particularly important to patients with “sick sinus syndrome” or other supraventricular cardiac conduction conditions, such as sinoatrial or atrioventricular block.

There have been reports of syncope and seizures. In investigating such patients the possibility of heart block or long sinusal pauses should be considered.

Gastrointestinal conditions

Peptic ulcer/ GI bleeding [1-4], [2-7], [3-8]*:* Patients at increased risk for developing ulcer or GI bleeding, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs), should be monitored for symptoms. However, the clinical studies with donepezil hydrochloride 5 to 10 mg/day showed no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Nausea/ Vomiting [2-8]*:* Donepezil hydrochloride, as a predictable consequence of its pharmacological properties, produced diarrhea, nausea, and vomiting. Although in most case, these effects were mild and transient, sometimes lasting 1 to 3 weeks, and resolved during continued use of donepezil hydrochloride, closely observe patients at the initiation of treatment and after dose increases.

Genitourinary [1-7], [2-9], [3-9]*:* Although not observed in clinical trials of donepezil hydrochloride, cholinomimetics may cause bladder outflow obstruction.

Neurological conditions [1-8], [2-10], [3-10]*:* Seizures: Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity may also be a manifestation of Alzheimer's disease. Cholinomimetics may have the potential to exacerbate or induce extrapyramidal symptoms.

Pulmonary conditions [1-6], [2-11], [3-11]*:* Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease.

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

Severe hepatic impairment [3-12]*:* There are no data for patients with severe hepatic impairment.

[1-3]- [1-8] เอกสารอ้างอิง 1 :AHFS Drug Information 2012 หน้า 1265 หมายเลข 3-8

[2-6]- [2-11] เอกสารอ้างอิง 2 :Drug Facts and Comparison 2012 หน้า 1681 หมายเลข 6-11

[3-5]- [3-12] เอกสารอ้างอิง 3 : เอกสารกำกับยาต้นแบบที่ได้รับอนุมัติจากอย. หมายเลข 5-13

10. INTERACTIONS WITH OTHER MEDICAMENTS [2-13], [3-14]

Donepezil hydrochloride and/or any of its metabolites do not inhibit the metabolism of theophylline, warfarin, cimetidine or digoxin in humans. The metabolism of donepezil hydrochloride is not affected by concurrent administration of digoxin or cimetidine.

In vitro studies have shown that the cytochrome P450 isoenzymes 3A4 and to a minor extent 2D6 are involved in the metabolism of donepezil hydrochloride. Drug interaction studies performed *in vitro* show that ketoconazole and guanidine, inhibitors of CYP3A4 and 2D6 respectively, inhibit donepezil hydrochloride metabolism. Therefore, these and other CYP3A4 inhibitors, such as itraconazole and erythromycin, and CYP2D6 inhibitors, such as fluoxetine could inhibit the metabolism of donepezil hydrochloride. In a study in healthy volunteers, ketoconazole increased mean donepezil hydrochloride concentrations by about 30%. Moreover, CYP-450 3A4 and 2D6 inducers such as rifampicin, phenytoin, carbamazepine and alcohol may reduce the levels of donepezil hydrochloride. Since the magnitude of an inhibiting or inducing effect is unknown, such drug combinations should be used with care.

Donepezil hydrochloride has the potential to interfere with medications having anticholinergic activity such as atropine. There is also the potential for synergistic activity with concomitant treatment involving medications such as succinylcholine, other neuro-muscular blocking agents, cholinergic agonists such as bethanechol, beta blocking agents which have effects on cardiac condition or aspirin/ NSAIDs such as ibuprofen, or naproxen may increase the risk of developing stomach ulcers.

[2-13] เอกสารอ้างอิง 2 : Drug Facts and Comparison 2012 หน้า 1681-2 หมายเลข 13

[3-14] เอกสารอ้างอิง 3 : เอกสารกำกับยาต้นแบบที่ได้รับอนุมัติจากอย. หมายเลข 14

11. PREGNANCY AND LACTATION [3-15]

Pregnancy:

Category C [4-1] according to US pregnancy category; either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

Teratology studies conducted in pregnant rats at doses up to approximately 80 times the human dose and in pregnant rabbits at doses up to approximately 50 times the human dose did not disclose any evidence for a teratogenic potential. However, in a study in which pregnant rats were given approximately 50 times the human dose from day 17 of gestation through day 20 postpartum, there was a slight increase in stillbirths and a slight decrease in pup survival through day 4 postpartum. No effect was observed at the next lower dose tested, approximately 15 times the human dose. Donepezil hydrochloride should not be used during pregnancy because no clinical data of it on exposed pregnancies are available.

Lactation [2-12]:

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

[2-12] เอกสารอ้างอิง 2 :Drug Facts and Comparison 2012 หน้า 1681 หมายเลข 12

[3-15] เอกสารอ้างอิง 3 : เอกสารกำกับยาต้นแบบที่ได้รับอนุมัติจากอย. หมายเลข 15

12. UNDESIRABLE EFFECTS [3-17]

The most common adverse events are diarrhea, muscle cramps, fatigue, nausea, vomiting, anorexia, 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. The table below reflects the incidence of adverse events in patients receiving treatment with donepezil hydrochloride for all stages of 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) and rare (>1/10,000, <1/1,000).

System Organ Class	Very Common	Common	Uncommon	Rare
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
Gastrointestinal disorders	Diarrhea Nausea	Vomiting Abdominal disturbance	Gastrointestinal haemorrhage Gastric and duodenal ulcers	

System Organ Class	Very Common	Common	Uncommon	Rare
Hepato-biliary disorders				Liver dysfunction including hepatitis***
Skin and subcutaneous tissue disorders		Rash Pruritis		
Musculoskeletal, connective tissue and bone disorders		Muscle cramps		
Renal and urinary disorders		Urinary incontinence		
General disorders and administration site conditions	Headache	Fatigue Pain		
Investigations			Minor increase in serum concentration of muscle creatine kinase	
Injury and poisoning		Accident		

*In investigating patients for syncope or seizure the possibility of heart block or long sinusal pauses should be considered (see section 9).

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

***In cases of unexplained liver dysfunction, withdrawal of donepezil hydrochloride should be considered.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE [3-16]

Donepezil hydrochloride has minor to moderate influence in the ability to drive and use machines.

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

[3-16]- [3-17] เอกสารอ้างอิง 3 : เอกสารกำกับยาต้นแบบที่ได้รับอนุมัติจากอย. หมายเลข 16-17

13. OVERDOSE AND TREATMENT [3-18]

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

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

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

[2-14] เอกสารอ้างอิง 2 :Drug Facts and Comparison 2012 หน้า 1683 หมายเลข 14

[3-18] เอกสารอ้างอิง 3 :เอกสารกำกับยาต้นแบบที่ได้รับอนุมัติจากอย. หมายเลข 18

14. STORAGE CONDITION

Store in tight containers at temperatures below 30°C.

15. DOSAGE FORMS AND PACKAGING AVAILABLE

5 mg tablets; 10 mg tablets: aluminium-clear colorless PVC/PVdC blister of 14 tablets packed in paper carton.

16. NAME AND ADDRESS OF MANUFACTURER

T.O. CHEMICALS(1979) Ltd.

280 Soi Sabaijai, Suthisarn Road, Bangkok 10310

Tel. 02-2756053-9 Fax. 02-2777350

17. DATE OF REVISION OF PACKAGE INSERT

10 May 2016