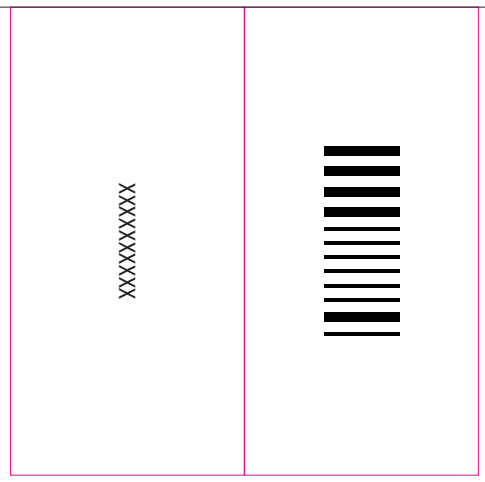

For the use of a registered medical practitioner or a hospital or a laboratory only

JUBDOZIL
(Donepezil Hydrochloride Tablets 5 mg)
JUBDOZIL
(Donepezil Hydrochloride Tablets 10 mg)

PRODUCT NAME:
JUBDOZIL (Donepezil Hydrochloride Tablets 5 mg)
JUBDOZIL (Donepezil Hydrochloride Tablets 10 mg)

NAME AND STRENGTH OF ACTIVE INGREDIENT:
Each film-coated tablet of:
Jubdozil (Donepezil Hydrochloride Tablets 5 mg) contains Donepezil hydrochloride 5 mg
Jubdozil (Donepezil Hydrochloride Tablets 10 mg) contains Donepezil hydrochloride 10 mg

PRODUCT DESCRIPTION:
Donepezil Hydrochloride Tablets 5mg
White to off-white, round, film-coated tablets, debossed with '**J**' on one side and '**5**' on the other.
Donepezil Hydrochloride Tablets 10mg
White to off-white, round, film-coated tablets, debossed with '**J**' on one side and '**10**' on the other.

PHARMACODYNAMICS / PHARMACOKINETICS:
Pharmacodynamic properties:
Pharmacotherapeutic groups: Anti-dementia drugs; Anticholinesterase; ATC Code: N06DA02. Donepezil hydrochloride is a reversible inhibitor of acetylcholinesterase, the predominant cholinesterase in the brain. Donepezil hydrochloride is over 1000 times more potent an inhibitor of this enzyme than of butyrylcholinesterase, an enzyme which is present mainly outside the central nervous system.

Mechanism of Action
Current theories on the pathogenesis of the cognitive signs and symptoms of Alzheimer's disease attribute some of them to a deficiency of cholinergic neurotransmission. Donepezil hydrochloride is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. There is no evidence that donepezil alters the course of the underlying process.

Pharmacokinetics Absorption:
Oral administration of Donepezil tablets produces predictable plasma concentrations with maximal values achieved approximately 3 to 4 hours after dose 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
the 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 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-labelled donepezil hydrochloride, approximately 28% of the label remained unrecovered.
This suggests that donepezil hydrochloride and/or any of 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 - labelled 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 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.

INDICATION:
Donepezil tablets are indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia..

RECOMMENDED DOSE:

Adults/Elderly:
Treatment is initiated at 5 mg/day (once-a-day dosing). Donepezil should be taken orally, in the evening, just prior to retiring.
The 5 mg/day dose should be maintained for at least one month in order to allow the earliest clinical responses to treatment to be assessed and to allow steady-state concentrations of donepezil hydrochloride to be achieved. Following a one-month clinical assessment of treatment at 5 mg/day, the dose of Donepezil tablet 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 Donepezil is seen.

Renal & Hepatic Impairment:
A similar dose schedule can be followed for patients with renal impairment, as clearance of donepezil hydrochloride is not affected by this condition. Due to possible increased exposure in mild to moderate hepatic impairment, dose escalation should be performed according to individual tolerability. There are no data for patients with severe hepatic impairment.

MODE OF ADMINISTRATION:
Donepezil hydrochloride tablet should be taken orally.

CONTRA-INDICATION:
Donepezil is contraindicated in patients with a known hypersensitivity to donepezil hydrochloride, piperidine derivatives, or to any excipients used in the formulation.
The safety of Donepezil in pregnancy and lactation has not been established. Donepezil is not recommended for use in children.

WARNINGS AND PRECAUTIONS:
Treatment should be initiated and supervised by a doctor experienced in the diagnosis and treatment of Alzheimer's dementia. Maintenance treatment can be continued for as long as a therapeutic benefit for the patient exists. Therefore, the clinical benefit of Donepezil should be reassesed on a regular basis. Discontinuation should be considered when evidence of a therapeutic effect is no longer present. Individual response to Donepezil cannot be predicted.
The use of Donepezil in patients with severe Alzheimer's dementia, other types of dementia or other types of memory impairment (e.g. age related cognitive decline), has not been established.
Anaesthesia: Donepezil, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine- type muscle relaxation during anaesthesia.
Cardiovascular Conditions: Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate (e.g. bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome"or other supraventricular cardiac conduction conditions such as sinoatrial or atrioventricular block. Syncopal episodes have been reported in association with the use of Donepezil.
Gastrointestinal Conditions: 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 of developing ulcers. e.g. those with a history of ulcer disease or those receiving concurrent nonsteriodal anti-inflammatory drugs (NSAIDS). Clinical studies of Donepezil tablets have shown 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, appeared more frequently with the 10 mg/day dose than with the 5 mg/day dose. In most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of Donepezil.
Genitourinary: Although not observed in clinical trials of Donepezil tablets, 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.
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 tablets concomitantly with other inhibitors of acetylcholinesterase, agonists or antagonists of the cholinergic system should be avoided.

Last modified: 9. September 2020, 4:49 PM
Black

Reason for Artwork: New	JUBILANT GENERICS	**Dimension: 310 x 240 mm**
Item Code: XXXXXXXXXX		**Superseded Item Code: NA**
Substrate: 40 GSM Bible paper with folding size 62 x 31 mm		

Site Packaging Development Sign and Date		**Production Sign and Date**		**QA Sign and Date**	

XXXXXXXXX

Mfg. Lic. No.: 58/UA/2007

Effects on ability to drive and use machines

Donepezil has minor or moderate influence on the ability to drive and use machines.

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

INTERACTIONS WITH OTHER MEDICAMENTS:

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.

Donepezil hydrochloride has the potential to interfere with medications having anticholinergic activity.

There is potential for synergistic activity with concomitant treatment involving medications such as succinylcholine, other neuro-muscular blocking agents or cholinergic agonists.

Concurrent use of donepezil and succinylcholine may result in prolonged neuromuscular blockade.

No adverse effects related to drug interactions were reported when patients were concomitantly administered donepezil and selective serotonin reuptake inhibitors, neuroleptics or (in a small number of cases) anti-Parkinsonian treatment.

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.

Concurrent use of donepezil and oxybutynin may result in decreased efficacy of the cholinesterase inhibitor.

Concurrent use of donepezil and tolterodine may result in decreased efficacy of the cholinesterase inhibitor.

Concurrent use of donepezil and ramelteon may result in increased ramelteon exposure.

Concurrent use of donepezil and bethanechol may result in cholinergic adverse effects (bradyarrhythmia, bronchospasm, hyperhidrosis, diarrhea, vomiting).

Concurrent use of donepezil and quinidine may result in increased donepezil bioavailability.

Concurrent use of donepezil and ketoconazole may result in increased donepezil bioavailability.

Other CYP3A4 inhibitors, such as itraconazole and erythromycin, and CYP2D6 inhibitors, such as fluoxetine could inhibit the metabolism of donepezil.

There is also the potential for synergistic activity with concomitant treatment involving beta blocking agents which have effects on cardiac conduction.

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. The potential risk for humans is unknown.

Donepezil hydrochloride 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.

UNDESIRABLE EFFECTS:

Cardiovascular: hypertension, rare cases of angina, bradycardia , atrioventricular block, torsades de pointes, sino-atrial block, bradycardia

Endocrine metabolic: weight decreased, anorexia

Gastrointestinal: diarrheoa, loss of appetite, nausea, vomiting, gastrointestinal hemorrhage, abdominal pain, dyspepsia, gastric and duodenal ulcers

Hematologic: contusion, ecchymosis Skin: rash, pruritus,

Hepatic: Increased liver transaminases, liver dysfunction including hepatitis Musculoskeletal: muscle cramps, increased creatine kinase level

Neurologic: asthenia, dizziness, headache, insomnia, somnolence, seizures, syncope, extrapyramidal symptoms

Psychiatric: depression, dream disorder, hallucinations, agitation, aggressive behaviour, confusion

Renal and urinary disorders: urinary incontinence, urinary-tract infections Other: fatigue, upper-respiratory-tract infections, sweating

OVERDOSE AND TREATMENT:

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

Overdosage with cholinesterase inhibitors can result in cholinergic crisis 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.

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

hydrochloride and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration).

STORAGE CONDITION:

Store below 30°C. Keep out of the reach of children.

DOSAGE FORMS AND PACKAGING AVAILABLE:

Film-coated tablet

Blister strip of 3x10 Tablets

NAME AND ADDRESS OF MANUFACTURER

Jubilant Generics Limited.
Village Sikandarpur Bhainswal,
Roorkee-Dehradun Highway,
Bhagwanpur, Roorkee, Distt- Haridwar,
Uttarakhand-247661 India

Product registration holder:

Synerrv Sdn Bhd, SO-29-2, MENARA 1,
KL ECO CITY, JALAN BANGSAR,
KG HAJI ABDULLAH HUKUM,
59200 KUALA LUMPUR, MALAYSIA

DATE OF REVISION OF PACKAGE INSERT

September, 2020

Last modified: 9. September 2020, 4:49 PM

Black

Reason for Artwork: New			**Dimension: 310 x 240 mm**		
Item Code: XXXXXXXXXX			**Superseded Item Code: NA**		
Substrate: 40 GSM Bible paper with folding size 62 x 31 mm					
Site Packaging Development Sign and Date		**Production Sign and Date**		**QA Sign and Date**	