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

# JUBDOZIL
## Donepezil 5 mg and 10 mg tablets

**PRODUCT NAME:**
JUBDOZIL FILM COATED TABLET 5MG
JUBDOZIL FILM COATED TABLET 10MG

**NAME AND STRENGTH OF ACTIVE INGREDIENT:**

Each film-coated tablet contains:

Donepezil hydrochloride 5 mg equivalent to 4.56 mg of Donepezil free base.
Donepezil hydrochloride 10 mg equivalent to 9.12 mg of Donepezil free base.

**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.

**EXCIPIENTS:** Lactose monohydrate, Cellulose microcrystalline, Maize starch, Low substituted Hydroxypropyl cellulose, Magnesium stearate

**PHARMACODYNAMICS / PHARMACOKINETICS:**

Pharmacodynamic properties:

Pharmcotherapeutic group: 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.

In patients with Alzheimer's Dementia participating in clinical trials, administration of single daily doses of 5 mg or 10 mg of Donepezil tablet 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 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.

**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 it's metabolites may persist in the body for more than 10 days.

**Metabolism / Excretion:**

Donepezil Hydrochloride 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.

Donepezil Hydrochloride is metabolized by CYP 450 isoenzymes 2D6 and 3A4 and undergoes to glucuronidation. Following administration of 14C labeled donepezil hydrochloride, plasma radioactivity expresses as a percent of the administered dose, was present, primarily as intact, donepezil hydrochloride (53%) and as 6-O-desmethyl donepezil (11%), which has been reported to inhibit ACHE to the same extent, as donepezil hydrochloride invitro and was found in plasma at concentration equal to about 20% of donepezil hydrochloride. Approximately 57% and 15% of total radioactivity recovered in urine and feces, respectively, over a period of 10 days, while 28% remained unrecovered, with about 17% of donepezil hydrochloride dose recovered in urine as unchanged drug. Examination of the effect of CYP2D6 genotype Alzheimer's patients showed differences in clearance value among CYP2D6 genotype subgroups. When compared to the extensive metabolizer, poor metabolizers had a 31.5% slower clearance and ultra-rapid metabolizer had a 24% faster clearance. These results suggest CYP2D6 has minor role in metabolism of donepezil hydrochloride.

**INDICATION:**

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

**RECOMMENDED DOSE:**

**Adults/Elderly:**

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 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 tablets 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 scheduled can be followed for patients with renal impairment as clearance of donepezil hydrochloride is not affected by this condition.

Due to possible increase of exposure in mild to moderate hepatic impairment, dose escalation should be performed according to individual tolerability. There are no data for patient with severe hepatic impairment.

**MODE OF ADMINISTRATION:**

Donepezil hydrochloride tablets 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.

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

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.

*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).

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 generalized convulsion however seizures activity may also be a manifestation of Alzheimer's disease. Cholinomimetics may have the potential to exacerbate or induce extrapyramidal symptoms.

*Weight loss:* weight loss was reported as an adverse event in 4.7% of patient assigned Donepezil Hydrochloride 23 mg Tablets compared to 2.5% patient assign to 10mg Donepezil Hydrochloride. Compared to base line weights 8.4% of patients in Donepezil Hydrochloride Tablets 23 mg group were found to have a weight decrease of ≥ 7% by the end of the study, while 4.9% of group taking 10mg Donepezil Hydrochloride were found to have weight loss of ≥ 7% at the end of the study.

*Neurologic:* Neuroleptic Malignant Syndrome (NMS): there have been very rare post marketing reports of Neuroleptic Malignant Syndrome in patient treated with Donepezil Hydrochloride Tablets with or without concomitant antipsychotic medication. NMS is a potentially life threatening condition characterized by hyperthermia, muscle rigidity, autonomic in stability (eg- irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia), altered consciousness and elevated serum creatinine phosphokinase (CPK level). Addition sign may include myoglobinuria (Rhabdomyolysis) and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever in the absence of additional clinical manifestation of NMS, Donepezil Hydrochloride Tablets should be discontinued.

*Rhabdomyolysis (Muscle effects):* Rare cases of Rhabdomyolysis (including acute renal failure) have been reported in patients treated with Donepezil Hydrochloride Tablets, particularly in the days following dose initiation and dose increase. Majority of these cases occurred independently of Neuroleptic Malignant Syndrome (NMS). Patients should be carefully monitored for muscle pain, tenderness or weakness and darkened urine, particularly if accompanied by malaise or fever. Blood creatine phosphokinase (CPK) levels should be assessed in patient experiencing these symptoms. Donepezil Hydrochloride Tablet therapy should be discontinued if markedly elevated CPK levels are measured and/or if the patient develop signs and symptoms indicative of rhabdomyolysis. Although the decision to discontinue Donepezil Hydrochloride Tablet should be made based on the clinical judgement of the treating physician, in most post-marketing cases, therapy was withdrawn when CPK levels were 5X upper limit of normal or higher. Caution should be particularly exercised in prescribing Donepezil Hydrochloride Tablet to patients with predisposing/risk factors such as prior history of muscular disorders, uncontrolled hypothyroidism, hepatic or renal impairment, and in patients who are receiving concomitant medications that can cause rhabdomyolysis (e.g., statins, antipsychotics, selective serotonin reuptake inhibitor/serotonin norepinephrine reuptake inhibitor).

*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.

**INTERACTIONS WITH OTHER MEDICAMENTS:**

*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 CYP2D6 (e.g. imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean Ki about 50-130 microM), 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.

*Effect of other drugs on the metabolism of Donepezil:*

Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil hydrochloride metabolism in vitro. Whether there is a clinical effect of quinidine is not known. In a 7-day crossover study in 18 healthy volunteers, ketoconazole (200mg q.d.) increased mean donepezil hydrochloride (5mg q.d.) concentrations (AUC0-24 and Cmax) by 36%. The clinical relevance of this increase in concentration is unknown.

A small effect of CYP2D6 inhibitors was identified in a population pharmacokinetic analysis of donepezil hydrochloride concentrations measured in patients with Alzheimer's disease. Donepezil hydrochloride clearance was reduced by approximately 17% in patients taking 10 or 23 mg in combination with known CYP2D6 inhibitor. The results is consistent with the conclusion that CYP2D6 is a minor metabolic pathway of donepezil hydrochloride.

Inducers of CYP2D6 and CYP3A4 (e.g. phenytoin, carbamazepine, dexamethasone, rifampin and phenobarbital) could increase the rate of elimination of donepezil hydrochloride tablets.

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

*Use with anticholinergics:* Because of there mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

*Use of cholinomimetics and other cholinesterase inhibitors:* A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

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)

**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.

**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.

**UNDESIRABLE EFFECTS:**

The most common adverse events are diarrhoea, muscle cramps, fatigue, nausea, vomiting and Insomnia.

Adverse reactions reported as more than an isolated case as listed below. By system organ class and by frequency. Frequencies are defined as: common (> 1/100, <1/0), Uncommon (> 1/1,000, <1/100) and rare (> 1/10,000, <1 /1, 000).

| System Organ Class | Common | Uncommon | Rare |
|---|---|---|---|
| infections and infestations | Common cold | | |
| Metabolism and nutrition disorders | Anorexia | | |
| Psychiatric disorders | Hallucinations**<br>Agitation*<br>Aggressive behaviour** | | |
| Nervous system disorder | Syncope *<br>Dizziness<br>Insomnia | Seizure* | Extrapyramidal symptoms, Neuroleptic Malignant Syndrome (NMS) |
| Cardiac disorder | | **Bradycardia** | Sino-atrial block<br>Atrioventricular block<br>Frequency not known: Polymorphic ventricular tachycardia including<br>Torsades de Pointes; Electrocardiogram QT interval prolonged |
| Gastrointestinal disorders | Diarrhoea<br>Vomiting<br>Nausea<br>Abdominal disturbance | Gastrointestinal haemorrhage<br>Gastric and duodenal ulcers | |
| Hepalo bilary disorders | | | Liver dysfunction including hepatitis*** |
| Skin and subcutaneous tissue disorders | Rash<br>Pruritis | | |
| Musculoskeletal connective tissue and bone disorders | Muscle cramps | | Rhabdomyolysis |
| Renal and urinary disorders | Urinary Incontinence | | |
| General disorders and administration site conditions | Headache<br>Pain<br>Fatigue | | |
| Investigations | | Minor increase in<br>Serum concentration of muscle creatine kinase | |
| Injury and poisining | Accidents including falls | | |

*In investigating patients for syncope or seizure, the possibility of heart blocking 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 Hydrochloride Tablet should be considered.

**Adverse Events Leading to Discontinuation**

The rate of discontinuation from a controlled clinical trial of Donepezil Hydrochloride Tablet Film-coated Tablets 23 mg due to adverse events was higher (18.6%) than for the donepezil hydrochloride 10 mg/ day treatment group (7.9%).

The most common adverse events leading lo discontinuation, defined as those occurring in at least 1% of patients and greater than those occurring with donepezil hydrochloride 10 mg/day doses, are shown in Table 1:

| Table 1: Most Frequent Adverse Event Leading To Discontinuation From A Controller Clinical Trial By Treatment Group | | |
|---|---|---|
| Dose Group | 23 mg/day Donepezil Hydrochloride Tablet | 10 mg/day Donepezil Hydrochloride Tablet |
| Safely Population | 963 | 471 |
| Event/ % Discontinuing | | |
| Vomiting | 3 | 0 |
| Diarrhoea | 2 | 0 |
| Nausea | 2 | 0 |
| Dizziness | 1 | 0 |

The majority of discontinuations due to adverse events in the Donepezil Hydrochloride Tablet Film-coated Tablets 23 mg group occurred during the first month of treatment.

**Most Frequent Adverse Clinical Events Seen in Association with the Use of Donepezil Hydrochloride Tablet Film-coated Tablets 23 mg**

The most common adverse events, defined as those occurring at a frequency of at least 5%, include nausea, diarrhoea, vomiting, and anorexia. These adverse events were often of mild to moderate intensity.

**Adverse Events Reported in Controlled Trials**

The events cited reflect experience gained under closely monitored conditions of a controlled clinical trial in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behaviour, and the lands of patients treated may differ. Table 2 lists adverse events that were reported in at least 2% of patients who received 23 mg/day of Donepezil Hydrochloride Tablet and at a higher frequency than those receiving 10 mg/day of Donepezil Hydrochloride Tablet in a controlled clinical trial that compared the two doses. In this study, there were no important differences in the type of adverse events in patients taking Donepezil Hydrochloride Tablet with or without memantine.

| **Table 2 Adverse Events Reported in a Controlled Clinical Trial in Moderate to Severe Alzheimer's Disease in at Least 2% of Patients and Higher in the 23 mg/day Group** | | |
|---|---|---|
| **Body System/ Adverse Event** | **23 mg/day Donepezil Hydrochloride Tablet** | **10 mg/day Donepezil Hydrochloride Tablet** |
| Safely Population | 963 | 471 |
| Percent of Patients with any adverse events | 74 | 64 |
| Gastrointestinal disorders | | |
| Nausea | 12 | 3 |
| Vomiting | 9 | 3 |
| Diarrhoea | 8 | 5 |
| General disorders and administration site conditions | | |
| Fatigue | 2 | 1 |
| Asthenia | 2 | 1 |
| Injury, poisoning and procedural complications | | |
| Confusions | 2 | 0 |
| Investigations | | |
| Weight decrease | 5 | 3 |
| Metabolism and nutritional disorders | | |
| Anorexia | 5 | 2 |
| Nervous system | | |
| Dizziness | 5 | 3 |
| Headache | 4 | 3 |
| Somnolence | 2 | 1 |
| Psychiatric disorders | | |
| Insomnia | 3 | 2 |
| Renal and urinary disorders | | |
| Urinary incontinence | 3 | 1 |

**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.

**SHELF LIFE:** 24 Months

**DOSAGE FORMS AND PACKAGING AVAILABLE:**

Film-coated tablet

PVC/Alu Blister pack of 1x10's, 3x10's & 100x10's.

**NAME AND ADDRESS OF MANUFACTURER**

Jubilant Generics Ltd.
Village Sikandarpur Bhainswal,
Roorkee- Dehradun Highway,
Bhagwanpur, Roorkee,
District Haridwar, Uttarakhand 247 661, India

JUBILANT GENERICS

**Product Registrant:**

GOLDPLUS UNIVERSAL

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**DATE OF REVISION OF PACKAGE INSERT**

October, 2022