SUMMARY OF PRODUCT CHARACTRISTICS

1. NAME OF THE MEDICINAL PRODUCT
Aldrol 5 (Donepezil Hydrochloride Tablets USP 5 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Qualitative and Quantitative Composition
Label Claim:
Each film coated tablet contains: Donepezil Hydrochloride USP …...5 mg
Excipients…..... q.s

Excipient with known effect:
Each tablet contains 96.0 mg Lactose Monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL
Dosage form: Film coated tablets.

Description: White, round, biconvex, film coated tablets with 'D5' debossed on one side and plain on otherside.

4. CLINICAL PARTICULARS
4.1 Therapeutic indication(s)
Donepezil hydrochloride is indicated for the treatment of dementia of the Alzheimer's type. Efficacy has been demonstrated in patients with mild, moderate, and severe Alzheimer's disease. It is also used in vascular dementia.

4.2 Posology and method of administration
Adults/Elderly people
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 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 product 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.

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's dementia. Diagnosis should be made according to accepted guidelines (e.g. DSM IV, ICD 10). Therapy with donepezil 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 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 cannot be predicted. Upon discontinuation of treatment, a gradual abatement of the beneficial effects of

product is seen.

Paediatric population
Product is not recommended for use in children and adolescents below 18 years of age.

Patients with renal and 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 (see section 5.2), dose escalation should be performed according to individual tolerability. There are no data for patients with severe hepatic impairment.

Method of administration
Product should be taken orally, in the evening, just prior to retiring.

4.3 Contra-indications
Donepezil Hydrochloride Tablets USP 5 mg/10 mg is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to piperidine derivatives.

4.4 Special warnings and precautions for use
The use of product 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 investigated.

Anaesthesia
Product 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.

Gastrointestinal Conditions
Patients at increased risk for developing ulcers, 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 Product showed no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Genitourinary
Although not observed in clinical trials of A Product, 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 may have the potential to exacerbate or induce extrapyramidal symptoms.

Neuroleptic Malignant Syndrome (NMS)
NMS, a potentially life-threatening condition characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels, has been reported to occur very rarely in association with donepezil, particularly in patients also receiving concomitant antipsychotics. 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.

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

Severe Hepatic Impairment
There are no data for patients with severe hepatic impairment.

Mortality in Vascular Dementia Clinical Trials
Three clinical trials of 6 months duration were conducted studying individuals meeting the NINDS-AIREN criteria for probable or possible vascular dementia (VaD). The NINDS-AIREN criteria are designed to identify patients whose dementia appears to be due solely to vascular causes and to exclude patients with Alzheimer's disease. In the first study, the mortality rates were 2/198 (1.0%) on donepezil hydrochloride 5 mg, 5/206 (2.4%) on donepezil hydrochloride 10 mg and 7/199 (3.5%) on placebo. In the second study, the mortality rates were 4/208 (1.9%) on donepezil hydrochloride 5 mg, 3/215 (1.4%) on donepezil hydrochloride 10 mg and 1/193 (0.5%) on placebo. In the third study, the mortality rates were 11/648 (1.7%) on donepezil hydrochloride 5 mg and 0/326 (0%) on placebo. The mortality rate for the three VaD studies combined in the donepezil hydrochloride 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 hydrochloride 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. In pooled Alzheimer's disease studies (n=4146), and when these Alzheimer's disease studies were pooled with other dementia studies including the vascular dementia studies (total n=6888), the mortality

rate in the placebo groups numerically exceeded that in the donepezil hydrochloride groups.

Excipients
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
Effect of donepezil on the Metabolism of Other Drugs: No effects of donepezil on the pharmacokinetics of theophylline, cimetidine, warfarin, digoxin and ketoconazole were reported. Effect of Other Drugs on the Metabolism of donepezil: Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, are reported to inhibit donepezil metabolism in vitro.

Inducers of CYP 2D6 and CYP 3A4 (e.g., phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of donepezil.

Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications. A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol. In reported in vitro studies donepezil did not affect the binding of furosemide, digoxin, and warfarin to human albumin. Similarly, the binding of donepezil to human albumin was not affected by furosemide, digoxin and warfarin.

4.6 Fertility, pregnancy and lactation
Pregnancy
Pregnancy Category C: Donepezil should be used during pregnancy only if the potential benefitjustifies the potential risk to the fetus.

Nursing Mothers: It is not known whether donepezil is excreted in human milk. Caution should be exercised when donepezil is administered to a nursing woman.

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

4.8 Undesirable effects
The commonest symptoms are reported due to cholinomimetic properties of the drug. These include nausea, diarrhea, insomnia, vomiting, muscle cramp, fatigue and anorexia, often of mild intensity and transient, resolving during continued donepezil treatment without the need for dosemodification.

Others are:
Body as a Whole: Influenza, chest pain, toothache; fever, edema face, periorbital edema, hiatal hernia, abscess, cellulitis, chills, generalized coldness, head fullness, listlessness.

Cardiovascular System: hypertension, vasodilation, atrial fibrillation, hot flashes, hypotension; angina pectoris, postural hypotension, myocardial infarction, AV block (first degree), congestive heart failure, arteritis, bradycardia, peripheral vascular disease, supraventricular tachycardia, deep vein thrombosis.

Digestive System: fecal incontinence, gastrointestinal bleeding, bloating, epigastric pain; eructation, gingivitis, increased appetite, flatulence, periodontal abscess, cholelithiasis, diverticulitis, drooling, dry mouth, fever sore, gastritis, irritable colon, tongue edema, epigastric distress, gastroenteritis, increased transaminases, hemorrhoids, ileus, increased thirst, jaundice, melena, polydipsia, duodenal ulcer, stomach ulcer.

Endocrine System: diabetes mellitus, goiter.

Hemic and Lymphatic System: anemia, thrombocythemia, thrombocytopenia, eosinophilia, erythrocytopenia.

Metabolic and Nutritional Disorders: dehydration, gout, hypokalemia, increased creatine kinase, hyperglycemia, weight increase, increased lactate dehydrogenase.

Musculoskeletal System: bone fracture, muscle weakness, muscle fasciculation.

Nervous System: delusions, tremor, irritability, paresthesia, aggression, vertigo, ataxia, increased libido, restlessness, abnormal crying, nervousness, aphasia, cerebrovascular accident, intracranial hemorrhage, transient ischemic attack, emotional lability, neuralgia, coldness (localized), muscle spasm, dysphoria, gait abnormality, hypertonia, hypokinesia, neurodermatitis, numbness (localized), paranoia, dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing.

Respiratory System: dyspnea, sore throat, bronchitis, epistaxis, post nasal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, snoring.

Skin and Appendages: pruritus, diaphoresis, urticaria, dermatitis, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herpes zoster, hirsutism, skin striae, night sweats, skin ulcer.

Special Senses: cataract, eye irritation, blurred vision, dry eyes, glaucoma, earache, tinnitus, blepharitis, decreased hearing, retinal hemorrhage, otitis externa, otitis media, bad taste, conjunctival hemorrhage, ear buzzing, motion sickness, spots before eyes.

Urogenital System: urinary incontinence, nocturia, dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, pyelonephritis, inability to empty bladder, breast fibroadenosis, fibrocystic breast, mastitis, pyuria, renal failure, vaginitis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare providers are asked to report any suspected adverse reactions to the marketing authorization holder or if available via the national reporting system (See details below);

Paper based reporting: TMDA yellow card
Online reporting: https://sqrt.tmda.go.tz/
*USSD reporting: send a simple short text message to report any suspected Adverse Drug Reaction by dialing *152*00# and follow the instructions*.

4.9 Overdose

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. Tertiary anticholinergics such as atropine may be used as an antidote for donepezil overdosage. 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 and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-Alzheimer's ATC Code: N06DA02

Pharmacodynamics

Donepezil hydrochloride is a reversible inhibitor of the enzyme acetyl cholinesterase. It 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 dementing process.

5.2 Pharmacokinetic properties

Absorption: Reported evidences suggest maximum plasma levels were reached approximately 3 to 4 hours after oral administration. Plasma concentrations and area under the curve increased in proportion to the dose. Approximate steady-state was 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 affectthe absorption of donepezil hydrochloride.

Distribution: The reported steady state volume of distribution was 12 - 16 L/kg. Donepezil is approximately 96% bound to human plasma proteins, mainly to albumins (about 75%) and alpha1 - acid glycoprotein (about 21%) over the concentration range of 2-1000 ng/mL. Metabolism and elimination: The reported elimination half-life of donepezil is about 70 hours, and the mean apparent plasma clearance (Cl/F) is 0.13 - 0.19 L/hr/kg. Following multiple dose administration, donepezil is reported to accumulate in plasma by 4-7-fold, and steady state is reached within 15 days. 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. Donepezil is metabolized by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation.

Hepatic Disease: Reported evidence suggests that the clearance of donepezil hydrochloridedecreases by 20% in hepatic cirrhosis.

Renal Disease: Reported evidence suggests that there is no change in clearance of donepezilhydrochloride in moderate to severe renal impairment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core: Lactose Monohydrate (Super Tab 11 SD) USP-NF, Microcrystalline Cellulose (Avicel PH 112) USP-NF, Croscarmellose Sodium (Ac-Di-Sol) USP-NF, Magnesium Stearate USP-NF, Opadry II White 85F18422 IH, Purified Water USP.
Film coating: Polyvinyl Alcohol-Part. hydrolyzed (USP, FCC, Ph. Eur, JPE), Titanium dioxide (USP, FCC, Pht. Eur, JP, ChP, GB), Macrogol/PEG (USP, FCC, Ph. Eur, JECFA, JP), Talc (USP, FCC, Ph. Eur, JP, JECFA).

6.2 Incompatibilities

None known

6.3 Shelf-life

36 months

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture

6.5 Nature and contents of container

Aldrol 5 mg Tablets are packed in a carton containing 3 Alu PVC/PVDC blisters of 10 tabletsalong with pack insert.

6.6 Special precautions for disposal < and other handling

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

7. Name and Address of Marketing Authorization Holder
Unichem Laboratories Limited Unichem Bhavan, Prabhat Estate,
S.V. Road, Jogeshwari (West) Mumbai – 400102,
India.

8. Marketing Authorization Number
TAN 20 HM 0531

9. Date of First Registration / Renewal of the Registration
18/11/2020

10. Date of revision of the text