APRROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

PROPRIETARY NAME (AND DOSAGE FORM)

PRIFET 5 mg TABLETS (Tablet)

PRIFET 10 mg TABLETS (Tablet)

COMPOSITION

PRIFET 5 mg TABLETS:

Each film-coated tablet contains donepezil hydrochloride 5 mg. Contains lactose.

PRIFET 10 mg TABLETS:

Each film-coated tablet contains donepezil hydrochloride 10 mg. Contains lactose.

The other excipients in the formulations are pregelatinised starch, microcrystalline cellulose, hydroxypropylcellulose, magnesium stearate, hypromellose, polyethylene glycol, talc and titanium dioxide.

PRIFET 10 mg TABLETS also contains iron oxide yellow.

PHARMACOLOGICAL CLASSIFICATION

A 5.3 Cholinomimetics (cholinergics)

PHARMACOLOGICAL ACTION

Pharmacodynamics

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 butylcholinesterase, 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 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.

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. If this proposed mechanism of action is correct, donepezil's effect may lessen as the disease process advances and fewer cholinergic neurons remain intact. There is no evidence that donepezil alters the course of the underlying process.

The enzyme AChE also occurs peripherally in red blood cells, therefore, measurement of AChE activity in erythrocyte membranes provides an index for donepezil hydrochloride pharmacodynamics.

Pharmacokinetics

Absorption:

Oral administration of donepezil 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. Neither food nor time of administration (morning versus evening dose) affect the absorption of donepezil hydrochloride.

Distribution:

The steady-state volume of distribution is 12 l/kg. Donepezil hydrochloride is approximately 96 % 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 14C-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. The average CSF:plasma ratio for both doses, expressed as a percent of the concentration in plasma, was 15,7 %.

Metabolism / Excretion:

Donepezil is hepatically metabolised and the predominant route for the elimination of both the parent compound and its metabolites is renal, as 79 % of the recovered dose was found in the urine with the remaining 21 % in the faeces. Moreover, the parent compound, donepezil, is the predominant elimination product in urine. The major metabolites of donepezil include M1 and M2 (via O-dealkylation and hydroxylation), M11 and M12 (via glucuronidation of M1 and M2 respectively), M4 (via hydrolysis) and M6 (via N-oxidation).

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.

INDICATIONS

PRIFET TABLETS are indicated for the symptomatic treatment of mild or moderate dementia in Alzheimer's disease.

CONTRA-INDICATIONS

PRIFET TABLETS is contra-indicated in patients with a known hypersensitivity to donepezil hydrochloride, piperidine derivatives, or to any excipients used in the formulation.

The safety and efficacy of **PRIFET TABLETS** has not been established in children; therefore it is not recommended for use in children.

Pregnancy and lactation (see **"PREGNANCY AND LACTATION"**).

WARNINGS

Treatment should be initiated by a doctor experienced in the 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 **PRIFET TABLETS** should be reassessed on a regular basis. When evidence of a therapeutic effect is no longer present, discontinuation should be considered. Individual response to **PRIFET TABLETS** cannot be predicted.

The use of **PRIFET TABLETS** in patients with severe dementia, other types of dementia or other types of memory impairment (e.g. age related cognitive decline), has not been established.

Anaesthesia: PRIFET TABLETS, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia.

Cardiovascular Conditions: Due to their pharmacological action, **PRIFET TABLETS** 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: Gastric acid production may be promoted by **PRIFET TABLETS**. 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 non-steroidal 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: PRIFET TABLETS** may cause bladder outflow obstruction.

Neurological Conditions: PRIFET TABLETS are believed to have some potential to cause generalised convulsions. However, seizure activity may also be a manifestation of Alzheimer’s disease.

Pulmonary Conditions: Due to their cholinomimetic actions, **PRIFET TABLETS** should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. The administration of **PRIFET TABLETS** concomitantly with other inhibitors of acetylcholinesterase, agonists or antagonists of the cholinergic system should be avoided.

Patients recovering from bladder or gastrointestinal surgery: PRIFET TABLETS use is not recommended in patients recovering from bladder or gastrointestinal surgery.

INTERACTIONS

Medicines Highly Bound to Plasma Proteins:

Medicine displacement studies have been performed in vitro between this highly bound medicine (96 %) and other medicines such as furosemide, digoxin and warfarin. **PRIFET TABLETS** at concentrations of 0,3 - 10 µg/ml does not affect the binding of furosemide (5 µg/ml), digoxin (2 µg/ml), and warfarin (3 µg/ml) to

human albumin. Similarly, the binding of **PRIFET TABLETS** to human albumin is not affected by furosemide, digoxin and warfarin.

*Effect of **PRIFET TABLETS** on the Metabolism of Other Medicines:*

No *in vivo* clinical trials have investigated the effect of **PRIFET TABLETS** on the clearance of medicines metabolised by CYP3A4 (e.g. cisapride) or by CYP2D6 (e.g. imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean Ki about 50 - 130 µM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference.

Whether **PRIFET TABLETS** has any potential for enzyme induction is not known.

Donepezil hydrochloride and/or any of its metabolites do not inhibit the metabolism of theophyline, warfarin, cimetidine, digoxin, thioridazine, risperidone and sertraline in humans. In a study of Parkinson's disease patients on optimal treatment with L-dopa/carbidopa, administration of donepezil for 21 days had no effects on L-dopa or carbidopa blood levels. In this study, no effects on motor activity were observed.

*Effects of Other Medicines on the Metabolism of **PRIFET TABLETS**:*

Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro*. Therefore these and other CYP3A4 inhibitors, such as itraconazole and erythromycin, and CYP2D6 inhibitors, such as fluoxetine could inhibit the metabolism of donepezil. Whether there is a clinical effect of these inhibitors is not known. In a study in healthy volunteers, ketoconazole increased mean donepezil concentrations by 30 %. These increases are smaller than those produced by ketoconazole for other agents sharing the CYP-3A4 pathway and are not likely to be clinically relevant. Administration of donepezil had no effect on the pharmacokinetics of ketoconazole. Inducers of CYP2D6 and CYP3A4 (e.g. phenytoin, carbamazepine, alcohol, dexamethasone, rifampicin and phenobarbital) could increase the rate of elimination of **PRIFET TABLETS**.

Formal pharmacokinetic studies demonstrated that the metabolism of donepezil is not significantly affected by concurrent administration of digoxin, cimetidine, thioridazine, risperidone or sertraline.

Use with anticholinergics:

PRIFET TABLETS have the potential to interfere with the activity of anticholinergic medications, because of their mechanism of action.

Use with Cholinomimetics and other Cholinesterase Inhibitors:

A synergistic effect may be expected when **PRIFET TABLETS** are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol or beta blocking agents

which have an effect on cardiac conduction, but an *in vitro* study showed that donepezil hydrochloride had minimal effects on hydrolysis of succinylcholine.

PREGNANCY AND LACTATION

The safety of **PRIFET TABLETS** in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

Adults/Elderly:

The recommended dosages of **PRIFET TABLETS** 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).

The 5 mg/day dose should be maintained for at least 4 – 6 weeks 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 **PRIFET 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 **PRIFET TABLETS** is seen. After abrupt discontinuation of therapy, there is no evidence of a rebound effect.

Renal and Hepatic Impairment:

A similar dose schedule can be followed for patients with renal or mild to moderate hepatic impairment as clearance of donepezil hydrochloride is not affected by these conditions.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Side-effects:

Infections and infestations:

Frequent:

Common cold, influenza

Metabolism and nutrition disorders:

Less frequent:

Dehydration, hyponatraemia

Psychiatric disorders:

Frequent:

Insomnia, abnormal dreams, agitation, delusions, depression, hallucinations

Less frequent:

Abnormal crying, aggressive behaviour, increased libido, irritability, nervousness, restlessness, confusion

Nervous system disorders:

Frequent:

Dizziness, headache, somnolence

Less frequent:

Aphasia, ataxia, paraesthaesia, syncope, tremor, seizure, extrapyramidal symptoms

Eye disorders:

Less frequent:

Cataract, eye irritation, blurred vision

Ear and labyrinth disorders:

Less frequent:

Vertigo

Cardiac disorders:

Less frequent:

Atrioventricular block, bradycardia, sinoatrial block, angina

Vascular disorders:

Less frequent:

Hot flushes, hypertension, hypotension, vasodilation

Respiratory, thoracic and mediastinal disorders:

Less frequent:

Dyspnoea, sore throat, bronchitis

Gastrointestinal disorders:

Frequent:

Diarrhoea, nausea, vomiting, anorexia, pancreatitis, faecal incontinence, abdominal disturbance

Less frequent:

Gastrointestinal haemorrhage, epigastric pain, bloating, toothache, duodenal ulcer, gastric ulcer

Hepato-biliary disorders:

Less frequent:

Hepatitis

Skin and subcutaneous tissue disorders:

Less frequent:

Diaphoresis, ecchymosis, pruritus, urticaria, rash

Musculoskeletal, connective tissue and bone disorders:

Frequent:

Muscle cramps, arthritis

Renal and urinary disorders:

Frequent:

Frequent urination

Less frequent:

Nocturia, urinary incontinence, urinary tract infection

General disorders and administrative site conditions:

Frequent:

Fatigue, pain

Less frequent:

Chest pain

Investigations:

Frequent:

Weight decrease

Less frequent:

Minor increases in serum concentrations of creatine kinase, increased liver transaminases

Injury and poisoning:

Less frequent:

Accident, bone fracture

Special Precautions:

The use of donepezil is associated with weight loss. Patients' weight should be monitored during treatment with **PRIFET TABLETS**.

Female patients are more susceptible to nausea, vomiting, anorexia and weight loss.

PRIFET TABLETS contains lactose and should not be given to patients with rare hereditary problems, or a history of galactose intolerance, Lapp-lactose deficiency or glucose-galactose malabsorption.

Effects on the ability to drive and use machines

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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 **PRIFET TABLETS** 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.

General supportive measures should be utilised. Tertiary anticholinergics such as atropine may be used as an antidote for **PRIFET TABLETS** 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).

IDENTIFICATION

PRIFET 5 mg TABLETS

White to off-white, circular, biconvex, film-coated tablets debossed with ‘X’ on one side and ‘11’ on the other side.

PRIFET 10 mg TABLETS

Yellow coloured, circular, biconvex, film-coated tablets debossed with ‘X’ on one side and ‘12’ on the other side.

PRESENTATION

PRIFET 5 mg TABLETS:

1) Blister Pack:

Tablets are packed in 250 micron clear PVC/25 micron PE/90 gsm PVdC and silver coloured printed 25 micron aluminium foil with 7 gsm heat seal lacquer.

Each blister contains 10 tablets.

Pack size: 30's – Each carton contains 3 blisters of 10 tablets each.

2) HDPE Container Pack:

Tablets are packed in 40 ml HDPE white container with white closure with induction sealing wad containing 1 no. of 1 gm silica gel sachet.

Each container contains 30 tablets.

Pack size: 30's - One HDPE container contains 30 tablets.

PRIFET 10 mg TABLETS:

1) Blister Pack:

Tablets are packed in 250 micron clear PVC/25 micron PE/90 gsm PVdC and silver coloured printed 25 micron aluminium foil with 7 gsm heat seal lacquer.

Each blister contains 10 tablets.

Pack size: 30's – Each carton contains 3 blisters of 10 tablets each.

2) HDPE Container Pack:

Tablets are packed in 40 ml HDPE white container with white closure with induction sealing wad containing 1 no. of 1 gm silica gel sachet.

Each container contains 30 tablets.

Pack size: 30's - One HDPE container contains 30 tablets.

STORAGE INSTRUCTIONS

Store at or below 25 ℃. Protect from light. Do not remove blisters from carton until required for use. Keep securitainer well-closed after use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

PRIFET 5 mg TABLETS: 44/5.3/0946

PRIFET 10 mg TABLETS: 44/5.3/0947

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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