APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S5

PROPRIETARY NAME AND DOSAGE FORM:

DOLIN 5 mg TABLETS (tablet)

DOLIN 10 mg TABLETS (tablet)

DOLIN 20 mg TABLETS (tablet)

COMPOSITION:

DOLIN 5 mg TABLETS:

Each film-coated tablet contains escitalopram oxalate equivalent to 5 mg escitalopram.

DOLIN 10 mg TABLETS:

Each film-coated tablet contains escitalopram oxalate equivalent to 10 mg escitalopram.

DOLIN 20 mg TABLETS:

Each film-coated tablet contains escitalopram oxalate equivalent to 20 mg escitalopram.

The other excipients in the formulation are: silicified microcrystalline cellulose, croscarmellose sodium, butylhydroxytoluene, butylhydroxyanisole, cellulose microcrystalline, colloidal anhydrous silica, talc, magnesium stearate.

Coating material: hypromellose, macrogol 400, titanium dioxide (CI no. 77891)

PHARMACOLOGICAL CLASSIFICATION:

A 1.2 Psychoanaleptics (antidepressants)

PHARMACOLOGICAL ACTIONS:

Pharmaodynamics

Escitalopram is a potent and selective inhibitor of serotonin (5-HT)-uptake.

Escitalopram has minimal effect on noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake. Escitalopram has no or very low affinity for a series of receptors including 5-HT_{1A}, 5-HT_2,

DA D_1 and D_2 receptors, α_1-, α_2-, β-adrenoceptors, histamine H_1, muscarininic, benzodiazepine and opioid receptors.

Pharmacokinetics:

Absorption

Absorption is independent of food intake; mean t_{max} is 4 hours after multiple dosing.

Distribution

The apparent volume of distribution ($V_{d,\beta}/F$) after oral administration is about 12 to 26 l/kg. The plasma protein binding of escitalopram is approximately 55 %.

Biotransformation

Escitalopram is metabolised in the liver to demethylated and didemethylated metabolites. Alternatively, the nitrogen may be oxidised to form a N-oxide metabolite. Both parent compound and metabolites are partly excreted as glucuronides. Unchanged escitalopram is the predominant compound in plasma. After multiple dosing the mean concentrations of the demethyl and didemethyl metabolites are usually 28-31 % and < 5 % of the escitalopram concentration, respectively. Biotransformation of escitalopram to the demethylated metabolite is mediated by a combination of CYP2C19, CYP3A4 and CYP2D6.

Elimination

The elimination half-life after multiple dosing is about 30 hours and the plasma clearance after oral administration (Cl_{oral}) is about 0, 6 l/min.

Escitalopram and major metabolites are assumed to be eliminated both by the hepatic (metabolic) and the renal routes with the major part of the dose excreted as metabolites in urine.

Hepatic clearance is mainly by the P450 enzyme system. CYP2C19 is the primary isoenzyme involved in the demethylation of escitalopram, followed by CYP3A4 and CYP2D6. There is linear pharmacokinetics. Steady state plasma levels are achieved in about 1 week. Average steady state concentrations of 50 nmol/l (range 20 to 125 nmol/ l) are achieved at a daily dose of 10 mg.

Elderly patients (> 65 years of age)

A longer half-life (about 50 %) and decreased clearance values, due to a reduced rate of metabolism, have been demonstrated in the elderly.

Reduced hepatic function

Escitalopam is eliminated more slowly in patients with reduced hepatic function. The half-life of escitalopram is twice as long in patients with hepatic impairment and steady state escitalopram concentrations at a given dose will be approximately twice as high as in patients with normal liver function.

Reduced renal function

Escitalopram is eliminated more slowly in patients with mild to moderate reduction of renal function with no major impact on the escitalopram concentrations in serum. At present no information is available for the treatment of patients with severely reduced renal function (creatinine clearance < 30 ml /min).

Polymorphism

Based on *in vitro* results with escitalopram, genetic polymorphism with respect to CYP2D6 is not known; with respect to CYP2C19, it may be of clinical relevance, as shown in limited number of patients.

INDICATIONS:

Treatment of major depressive episodes.

CONTRA-INDICATIONS:

Hypersensitivity to escitalopram or to any of the excipients.

Children under 18 years of age; as safety and efficacy have not been established in this population.

Patients with known QT interval prolongation or congenital long QT syndrome (see **WARNINGS AND SPECIAL PRECAUTIONS and INTERACTIONS**)

Medicinal products that are known to prolong QT interval (see **WARNINGS AND SPECIAL PRECAUTIONS and INTERACTIONS**)

Monoamine Oxidase Inhibitors: Cases of serious reactions have been reported in patients receiving serotonin selective reuptake inhibitor (SSRI) in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued an SSRI and have been started on a MAOI (see **INTERACTIONS**). Some cases presented with features resembling serotonin syndrome (see **SIDE EFFECTS:** Class reactions). **DOLIN** should not be used in combination with a MAOI.

DOLIN may be started 14 days after discontinuing treatment with a MAOI. At least 7 days should elapse after discontinuing **DOLIN** treatment before starting a MAOI.

WARNINGS AND SPECIAL PRECAUTIONS:

Warnings

QT interval prolongation: DOLIN have been found to cause a dose-dependent prolongation of the QT interval. Cases of QT interval prolongation, ventricular prolongation and ventricular dysrhythmia including torsade de pointes have been reported during the post-marketing period, predominantly in patients of female gender, with hypokalaemia, or with preexisting QT interval prolongation or other cardiac diseases.

Caution is advised in patients with significant bradycardia; or in patients with recent acute myocardial infarction or uncompensated heart failure.

Electrolyte disturbances such as hypokalaemia and hypomagnesaemia increase the risk of malignant dysrhythmia and should be corrected before treatment with **DOLIN** is started.

If patients with stable cardiac disease are treated, an ECG review should be considered before treatment is started.

If signs of cardiac dysrhythmia occur during treatment with **[PRODUCT NAME]**, the treatment should be withdrawn and an ECG should be performed.

Mania – DOLIN should be discontinued in any patient entering a manic phase. **DOLIN** should be used with caution in patients with a history of mania/hypomania.

Paradoxical anxiety - Some patients with panic disorder may experience increased anxiety symptoms at the start of treatment with **[PRODUCT NAME]**. This paradoxical reaction usually subsides within two weeks of continued treatment. A low starting dose is advised to reduce the likelihood of a paradoxical anxiogenic effect.

Seizures - DOLIN should be discontinued in any patient who develops seizures. **DOLIN** should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. **DOLIN** should be discontinued if there is an increase in seizure frequency.

Diabetes mellitus - In patients with diabetes mellitus treatment with **DOLIN** may alter glycaemic control, possibly due to improvement of depressive symptoms. The doses of insulin and/or oral hypoglycaemic medications may need to be adjusted.

Suicide - As an improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for the risk of suicide.

Haemorrhage - There have been reports of cutaneous bleeding abnormalities, such as ecchymoses and purpura, with escitalopram. Caution is advised in patients taking **[PRODUCT NAME]**, particularly in concomitant use with medicines known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory medicines (NSAIDs)), as well as in patients with a history of bleeding disorders.

ECT (electroconvulsive therapy) - There is limited published clinical experience of concurrent administration of **DOLIN** and ECT, therefore caution is advisable.

Risk of Serotonin syndrome

Co-administration with MAO inhibitors may cause serotonin syndrome.

Co-administration with other serotonergic medicines (e.g. tramadol, sumatriptan) as well as other antidepressants with serotonergic properties may lead to an enhancement of serotonin associated effects, e.g. the serotonin syndrome.

There have been reports of enhanced effects when escitalopram has been given with lithium or tryptophan and therefore concomitant use of **DOLIN** with these medicines should be undertaken with caution.

Special Precautions:

See **WARNINGS**.

Effects on ability to drive and use machines

DOLIN does not impair intellectual function or psychomotor performance.

Patients who are depressed and require treatment may have an impaired ability to drive or operate machinery. They should be warned of this possibility and advised to avoid such tasks if so affected.

INTERACTIONS:

Escitalopram has a low potential for clinically significant medicine interactions. *In vitro* studies have shown that the biotransformation of escitalopram to its demethylated metabolites depends on three parallel

pathways (cytochrome P450 (CYP) 2C19, 3A4 and 2D6). Escitalopram is a weak inhibitor of isoenzyme CYP1A2, 2C9, 2C19, 2E1, and 3A, and weak inhibitor of 2D6.

QT interval prolongation

Pharmacokinetic and pharmacodynamic studies of **DOLIN** combined with other medicinal products that prolong the QT interval have not been performed. An additive effect of escitalopram and these medicinal products cannot be excluded.

Therefore, co-administration of **DOLIN** with medicinal products that prolong the QT interval, such as Class 1A and Ill antidysrhmythics (e.g. amiodarone, quinidine), antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants (e.g. desimipramine, imipramine), certain antimicrobial agents (e.g. moxifloxacin, erythromycin IV, pentamidine, anti-malarial treatment particularly halofantrine), certain antihistamines (e.g. mizolastine) and anti-retrovirals (e.g. ritonavir, saquanivir, lopinavir), is contraindicated.

Ritonavir:

The pharmacokinetics of single doses of escitalopram were not changed by co-administration with a single dose of ritonavir (CYP3A4 inhibitor).

Ketoconazole:

Co-administration with ketoconazole (potent CYP3A4 inhibitor) has no effect on pharmacokinetics of **[PRODUCT NAME].**

Cimetidine:

Co-administration of racemic citalopram with cimetidine (potent CYP2D6, 3A4 and 1A2 inhibitor) resulted in increased plasma Concentrations of the racemate (43 % increase in AUC, 39 % increase in C_{max}). Thus, caution should be exercised at the upper end of the dose range of **DOLIN** when used concomitantly with high doses of cimetidine.

Monoamine Oxidase inhibitors (MAOI), Sumatriptan & Tramadol:

Co-administration with MAO inhibitors may cause serotonin syndrome.

Co-administration with other-serotonergic medicines (e.g. tramadol, sumatriptan) as well as other antidepressants with serotonergic properties may lead to an enhancement of serotonin associated effects, e.g. the serotonin syndrome.

There have been reports of enhanced effects when escitalopram has been given with lithium or tryptophan and therefore concomitant use of **DOLIN** with these medicines should be undertaken with caution (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Desipramine:

Co-administration with a single dose of desipramine (a CYP2D6 substrate) resulted in a twofold increase in plasma levels of desipramine. Therefore, caution is advised when **DOLIN** and desipramine are co-administered. A similar increase in plasma levels of desipramine, after administration of imipramine, was seen when given together with racemic citalopram.

Metoprolol:

Co-administration with a single dose of metoprolol 100 mg (a CYP2D6 substrate) resulted in a twofold increase in the C_{max} and a 52 % increase of the AUC of metoprolol. However, the combination had no clinically significant effects on blood pressure and heart rate.

Selegiline:

Racemic citalopram increased the AUC of selegiline by 29 %.

Other:

Pharmacokinetic interaction studies with racemic citalopram have demonstrated no clinically important interactions with carbamazepine (CYP3A4 substrate), triazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate) (single dose), warfarin (CYP3A4 and CYP2C9 substrate), levomepromazine (CYP2D6 inhibitor), lithium and digoxin.

However, prothrombin time was slightly increased after a single dose of 25 mg warfarin. The International Normalised Ratio (INR) needs to be carefully monitored in patients on the combination.

PREGNANCY AND LACTATION:

The safety of **DOLIN** in pregnant and lactating women has not been established.

DOSAGE AND DIRECTIONS FOR USE:

Adults

Major depressive episodes:

DOLIN should be administered as a single oral dose of 10 mg daily in otherwise healthy adults. Depending on individual patient response, the dose may be increased to a maximum of 20 mg daily.

Usually 2-4 weeks are necessary for an antidepressant response.

Elderly patients (> 65 years of age)

A longer half-life and a decreased clearance have been demonstrated in the elderly.

The maximum recommended dose for elderly patients is 10 mg daily.

Reduced renal function

Dosage adjustment is not necessary in patients with mild or moderate renal impairment.

No information is available on the treatment of patients with severely reduced renal function (creatinine clearance < 30 ml/min).

Reduced hepatic function

Dosages should be halved to the lower end of the dose range in patients with hepatic insufficiency.

The maximum recommended dose for adult patients with hepatic impairment is 10 mg daily.

DOLIN are administered as a single daily dose. **DOLIN** may be taken without regard to food intake

Serotonin withdrawal

When stopping **DOLIN** therapy, gradual dose reduction should be considered.

SIDE EFFECTS :

Adverse reactions observed with **DOLIN** are most frequent during the first one or two weeks of treatment and may decrease in intensity and frequency with continued treatment.

After prolonged administration abrupt cessation of **DOLIN** may produce withdrawal reactions in some patients.

Endocrine disorders

The following side effects have been reported and frequencies are unknown:

Inappropriate ADH secretion

Metabolism and nutrition disorders

Frequent:

Decreased appetite

Less frequent:

Hyponatraemia, weight loss, hyperprolactinaemia

Psychiatric disorders

Frequent:

Decreased libido, suicidal ideation, insomnia

The following side effects have been reported and frequencies are unknown:

Hallucinations, mania, confusion, agitation, anxiety, depersonalisation, panic attacks, nervousness.

Nervous system disorders

Frequent:

Dizziness, somnolence

The following side effects have been reported and frequencies are unknown:

Sleep disorder, seizures, tremor, movement disorders, drowsiness, taste disturbance, serotonin syndrome (typically characterised by a rapid onset of changes in mental state, with confusion, mania, agitation, hyperactivity, shivering, fever, tremor, ocular movements, myoclonus, hyperreflexia, and incoordination).

Cardiovascular disorders

Frequency unknown:

Electrocardiogram QT prolongation, ventricular dysrhythmia including torsade de pointes.

Eye disorders

The following side effects have been reported and frequencies are unknown:

Abnormal vision

Vascular disorders

The following side effects have been reported and frequencies are unknown:

Postural hypotension

Respiratory, thoracic and mediastinal disorders

Frequent:

Sinusitis, yawning

Gastrointestinal disorders

Frequent:

Constipation, diarrhoea, dry mouth, nausea.

The following side effects have been reported and frequencies are unknown:

Vomiting, anorexia, dyspepsia.

Hepato-biliary disorders

The following side effects have been reported and frequencies are unknown:

Abnormal liver function tests.

Skin and subcutaneous tissue disorders

Frequent:

Increased sweating.

The following side effects have been reported and frequencies are unknown:

Rash, ecchymoses, pruritus, alopecia, photosensitivity, urticaria, pyrexia.

Immune system disorders

The following side effects have been reported and frequencies are unknown:

Angioedema, anaphylactoid reactions

Musculoskeletal, connective tissue and bone disorders

The following side effects have been reported and frequencies are unknown:

Arthralgia, myalgia.

Renal and urinary disorders

The following side effects have been reported and frequencies are unknown:

Urinary retention.

Reproductive system and breast disorders

Frequent:

Ejaculation disorder, impotence, abnormal orgasm (female).

Less frequent:

Anorgasmia

The following side effects have been reported and frequencies are unknown:

Galactorrhoea

General disorders and administrative site conditions

Frequent:

Fatigue

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Treatment

There is no specific antidote. Treatment is supportive and symptomatic. Gastric lavage should be carried out as soon as possible after oral ingestion. Cardiac and vital signs monitoring are recommended along with general symptomatic supportive measures.

IDENTIFICATION:

DOLIN 5 mg TABLETS:

White to off–white coloured, round shaped, film-coated, biconvex tablets debossed with 'F' on one side and '53' on the other side.

DOLIN 10 mg TABLETS:

White to off–white coloured, oval shaped, film-coated, biconvex tablets debossed with 'F' on one side and '54' on the other side with a deep scoreline between '5' and '4'.

DOLIN 20 mg TABLETS:

White to off–white coloured, oval shaped, film-coated, biconvex tablets debossed with 'F' on one side and '56' on the other side with a deep scoreline between '5' and '6'.

PRESENTATION:

DOLIN 5 mg TABLETS / DOLIN 10 mg TABLETS / DOLIN 20 mg TABLETS:

1) **Blister Pack:**

   Tablets are packed in clear PVC film and printed aluminium foil. 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 white opaque HDPE containers with white opaque polypropylene closures with induction sealing wad. Each container contains 30 tablets.

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

STORAGE INSTRUCTIONS:

Store at or below 25 °C. The containers must be tightly closed.

Do not remove blisters from carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

DOLIN 5 mg: 44/1.2/0951.

DOLIN 10 mg: 44/1.2/0952.

DOLIN 20 mg: 44/1.2/0953.

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

Aurogen South Africa (Pty) Ltd

Woodhill Office Park, Building 1, 53 Phillip Engelbrecht Avenue

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