PROFESSIONAL INFORMATION FOR EMERDYNE TABLETS

SCHEDULING STATUS **S5**

1. NAME OF THE MEDICINE

EMERDYNE 10 mg (film-coated tablets)

EMERDYNE 20 mg (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

EMERDYNE 10 mg (film-coated tablets)

Escitalopram oxalate corresponding to 10 mg escitalopram.

Contains sugar. (104.33 mg of lactose monohydrate).

EMERDYNE 20 mg (film-coated tablets)

Escitalopram oxalate corresponding to 20 mg escitalopram.

Contains sugar. (208.67 mg of lactose monohydrate).

Excipients:

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

EMERDYNE 10 mg: A white to off white, circular, biconvex, film-coated tablet having “ML 60” debossed on one side, break line on opposite side and having notches on either ends of break line.

EMERDYNE 20 mg: A white to off white, circular, biconvex, film-coated tablet having “ML 61” debossed on one side, break line on opposite side and having notches on either ends of break line.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of major depressive episodes.

4.2 Posology and method of administration

Posology:

Adults:

Major Depressive episodes:

EMERDYNE 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 to obtain antidepressant response.

Elderly patients (> 65 years of age):

A longer half-life and a decreased clearance have been demonstrated in the elderly, therefore a lower initial and maximum dose should be considered.

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

Reduced renal function:

Dosage adjustment is not necessary in patients with mild to moderate renal impairment. No information is available on the treatment of patients with severely reduced renal function (creatinine clearance < 30 mℓ/min) (see Section 4.4).

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.

When stopping **EMERDYNE** therapy, gradual dose reduction should be considered. **EMERDYNE** is administered as a single daily dose.

Method of administration

EMERDYNE may be taken without regard to food intake.

4.3 Contraindications

- Hypersensitivity to escitalopram or to any of the other excipients of **EMERDYNE.**
- 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 Section 4.4 & 4.5).
- Medicinal products that are known to prolong QT interval (see Section 4.4 & 4.5).

Monoamine Oxidase Inhibitors:

Cases of serious reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued an SSRI and have been started on an MAOI (see Section 4.5). Some cases presented with features resembling serotonin syndrome (see Section 4.4 & 4.8: Class reactions). **EMERDYNE** should not be used in combination with an MAOI. **EMERDYNE** may be started 14 days after discontinuing treatment with an MAOI. At least 7 days should elapse after discontinuing **EMERDYNE** treatment before starting an MAOI.

4.4 Special warnings and precautions for use

QT interval prolongation

EMERDYNE has been found to cause a dose-dependent prolongation of the QT interval. Cases of QT interval prolongation and 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 pre-existing 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 **EMERDYNE** 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 **EMERDYNE**, the treatment should be withdrawn and an ECG should be performed.

Mania

EMERDYNE should be discontinued in any patient entering a manic phase.

EMERDYNE 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 **EMERDYNE.**

This paradoxical reaction usually subsides within two weeks during continued treatment. A low starting dose is advised to reduce the likelihood of a paradoxical anxiogenic effect.

Seizures

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

Diabetes mellitus

In patients with diabetes mellitus, treatment with **EMERDYNE** 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 during this period.

The possibility of a suicide attempt is inherent in depression and may persist until significant therapeutic effect is achieved.

Haemorrhage

There have been reports of cutaneous bleeding abnormalities, such as ecchymoses and purpura, with escitalopram. Caution is advised in patients taking **EMERDYNE**, 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 **EMERDYNE** and ECT, therefore caution is advisable.

Post-partum haemorrhage

There has been evidence of an association between antidepressants [particularly selective serotonin reuptake inhibitors (SSRIs) and serotonin non-selective reuptake inhibitors (SNRIs)] and post-partum haemorrhage (PPH). Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage PPH following SSRI/SNRI exposure within the month prior to birth. Healthcare professionals should be aware of the potential risk of PPH while making treatment decisions for prescribing SSRI/SNRI towards the end of pregnancy.

Patients should be advised to inform their doctors before taking SSRI/SNRI if they have history of bleeding disorders, such as von Willebrand disease (VWD) or haemophilia or if they are pregnant.

Excipients

Lactose intolerance

EMERDYNE contains lactose. Patients with rare hereditary problems of galactose intolerance and Lapp lactase deficiency, or glucose-galactose malabsorption should not take **EMERDYNE**.

4.5 Interaction with other medicines and other forms of interaction

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 isoenzymes CYP1A2, 2C9, 2C19, 2E1 and 3A, and a weak inhibitor of 2D6.

Ritonavir:

The pharmacokinetics of single doses of **EMERDYNE** is 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 the pharmacokinetics of **EMERDYNE**.

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 **EMERDYNE** when used concomitantly with high doses of cimetidine.

Monoamine Oxidase Inhibitors (MAOI's), Sumatriptan and 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.

Lithium and Tryptophan:

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

Desipramine:

Co-administration with a single dose of desipramine (a CYP2D6 substrate) resulted in a two-fold increase in plasma levels of desipramine. Therefore, caution is advised when **EMERDYNE** 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 two-fold 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 increases the AUC of selegiline by 29 %.

QT interval prolongation:

Pharmacokinetic and pharmacodynamic studies of **EMERDYNE** 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 **EMERDYNE** with medicinal products that prolong the QT interval, such as Class 1A and III antidysrhythmics (e.g. amiodarone, quinidine), antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants (e.g. desipramine, imipramine), certain antimicrobial agents (e.g. moxifloxacin, erythromycin IV, pentamidine, anti-malarial treatment particularly halofentrine), certain antihistamines (e.g. mizolastine) and anti-retrovirals (e.g. ritonavir, saquinavir, lopinavir), is contra-indicated.

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.

4.6 Fertility, pregnancy and lactation

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

4.7 Effects on ability to drive and use machines

Patients who are depressed and require treatment may have an impaired ability to drive or operate machinery. Furthermore, **EMERDYNE** can induce fatigue, dizziness, drowsiness and impair vision. The treating doctor should routinely evaluate the ability of patients on **EMERDYNE** to continue driving or operating complex machines.

4.8 Undesirable effects

Summary of the reported safety profile

Adverse reactions observed with **EMERDYNE** 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 **EMERDYNE** may produce withdrawal reactions in some patients.

Table 1: Tabulated summary of adverse events.

System organ class	**Frequency**	**Undesirable effect**
Blood and lymphatic system disorders	Frequency unknown	Thrombocytopenia
Immune system disorders	Frequency unknown	Angioedema, anaphylactic reaction
Endocrine disorders	Frequency unknown	Inappropriate ADH secretion
Metabolism and nutrition disorders	Frequent	Decreased appetite, increased appetite, weight increased

	Less frequent	Weight decreased, hyperprolactinaemia
	Frequency unknown	Hyponatraemia, inappropriate ADH secretion, anorexia
Psychiatric disorders	Frequent	Anxiety, restlessness, abnormal dreams, female and male: libido decreased, female: anorgasmia
	Less frequent	Bruxism, agitation, aggression
	Frequency unknown	Mania, suicidal ideation, suicidal behaviour, hallucinations, mania, confusion, agitation, anxiety, depersonalisation, panic attacks and nervousness, insomnia, suicidal ideation.
Nervous system disorders	Frequent	Insomnia, somnolence, sleep disorder, dizziness, paraesthesia, tremor
	Less frequent	Taste disturbance, syncope, serotonin syndrome
	Frequency unknown	Dyskinesia, movement disorder, convulsion, tremor, drowsiness, psychomotor restlessness/akathisia
Eye disorders	Less frequent	Mydriasis, visual disturbance
Ear and labyrinth disorders	Less frequent	Tinnitus
Cardiac disorders	Less frequent	Tachycardia, Bradycardia

	Frequency unknown	Electrocardiogram QT prolonged, ventricular dysrhythmia including torsade de pointes.
Vascular disorders	Frequency unknown	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Frequent	Sinusitis, yawning
	Less frequent	Epistaxis
Gastrointestinal disorders	Frequent	Nausea, diarrhoea, constipation, vomiting, dry mouth, taste disturbances
	Less frequent	Gastrointestinal haemorrhages (including rectal haemorrhage)
	Frequency unknown	Dyspepsia, vomiting, anorexia
Hepatobiliary disorders	Frequency unknown	Hepatitis, liver function test abnormal
Skin and subcutaneous tissue disorders	Frequent	Sweating increased
	Less frequent	Urticaria, alopecia, rash, pruritus
	Frequency unknown	Ecchymosis, angioedemas, photosensitivity
Musculoskeletal and connective tissue disorders	Frequent	Arthralgia, myalgia
Renal and urinary disorders	Frequency unknown	Urinary retention
Reproductive system and breast disorders	Frequent	Male: ejaculation disorder, impotence, decreased libido. Female: abnormal orgasm
	Less frequent	Female: metrorrhagia, menorrhagia
	Frequency unknown	Male: priapism, ejaculation disorder, anorgasmia.

		Female: galactorrhoea, post-partum haemorrhage
General disorders and administrative site conditions	Frequent	Fatigue, pyrexia Oedema

Cases of suicidal ideation and suicidal behaviours have been reported during escitalopram therapy or early after treatment discontinuation (see Section 4.4).

Cases of QT-prolongation have been reported during the post-marketing period, predominantly in patients with pre-existing cardiac disease.
QT-prolongation may lead to ventricular dysrhythmia and torsade de pointes.

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs. The mechanism leading to this risk is unknown.

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

The following symptoms, hostility, suicidal ideation and self-harm, have been reported in children being treated with antidepressants.

Post-marketing experience

There has been evidence of an association between antidepressants [particularly selective serotonin reuptake inhibitors (SSRIs) and serotonin non-selective reuptake inhibitors (SNRIs)] and post-partum haemorrhage (PPH). Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage PPH following SSRI/SNRI exposure within the month prior to birth. Healthcare professionals should be aware of the potential risk of PPH while making treatment decisions for prescribing SSRI/SNRI towards the end of pregnancy.
Patients should be advised to inform their doctors before taking SSRI/SNRI if they have history of bleeding disorders, such as von Willebrand disease (VWD) or haemophilia or if they are pregnant.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions & Quality Problem Reporting Form", found online under SAHPRA's publications: https://sahpra.org.za/wpcontent/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf

4.9 Overdose

(See Section 4.8)

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.

5. PHARMACOLOGICAL PROPERTIES

A 1.2 Psychoanaleptics (antidepressants)

5.1 Pharmacodynamic properties

Pharmacodynamic properties:

Escitalopram is a 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, muscarinic, benzodiazepine and opioid receptors.

5.2 Pharmacokinetic properties

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 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 the 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.

Special populations

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:

Escitalopram 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 a limited number of patients.

5.3 Preclinical safety data

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium, isopropyl alcohol, lactose monohydrate, magnesium stearate, propyl gallate, sodium carboxymethylcellulose, colloidal silicon dioxide, hydroxypropylmethylcellulose, titanium dioxide (E171), polyethylene glycol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months from the date of manufacture.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

The blisters are to be kept in the carton until required for use.

KEEP MEDICINE OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

EMERDYNE 10 mg

EMERDYNE 20 mg

Blister pack:

Tablets are packed in cold form laminate, 25 µm OPA/45 µm Aluminum foil/60 µm PVC as the forming material and plain 25 micron, aluminum foil, 6-8 gsm HSL, as the lidding material.

Aluminium blister pack of 3 x 10 (30) tablets. The blisters are placed in an outer carton.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd

Office Block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8. REGISTRATION NUMBER(S)

EMERDYNE 10 mg: 45/1.2/0881

EMERDYNE 20 mg: 45/1.2/0882

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 October 2013

10. DATE OF REVISION OF THE TEXT

06 March 2024