PROFESSIONAL INFORMATION

ZYTOMIL RANGE

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

ZYTOMIL 10 mg, film coated tablets

ZYTOMIL 20 mg, film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZYTOMIL 10 mg: Each coated tablet contains escitalopram oxalate equivalent to escitalopram 10 mg.

ZYTOMIL 20 mg: Each coated tablet contains escitalopram oxalate equivalent to escitalopram 20 mg.

For the full list of excipients, see section 6.1

ZYTOMIL tablets are sugar free.

3. PHARMACEUTICAL FORM

Coated tablets.

ZYTOMIL 10 mg: White, oval, coated tablet, debossed with ″E″ and ″C″ divided by a score on one side and “10” on the other side.

ZYTOMIL 20 mg: White, oval, coated tablet, debossed with ″E″ and ″C″ divided by a score on one side and “20” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZYTOMIL is indicated for the treatment of:

- major depressive episodes
- panic disorder with or without agoraphobia
- social anxiety disorder (social phobia)
- generalised anxiety disorder
- obsessive compulsive disorder (OCD).

4.2 Posology and method of administration

Posology

Adults:

Major depressive episodes:

ZYTOMIL 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.

Panic disorder with or without agoraphobia:

A single oral dose of 5 mg is recommended for the first week before increasing the dose to 10 mg daily. The dose may be further increased, up to a maximum of 20 mg daily, dependent on individual patient response. Maximum effectiveness is reached after about 3 months. The treatment lasts several months.

Social anxiety disorder:

Usual dosage is 10 mg once daily. The dose may be increased to a maximum of 20 mg daily depending on individual patient response.

Usually 2 - 4 weeks are necessary to obtain symptom relief. Treatment for 3 months is recommended to consolidate response. Long term treatment of responders for 6 months has been shown to prevent relapse and can be considered on an individual basis. Treatment benefits should be re-evaluated at regular intervals.

Generalised anxiety disorder:

Recommended dosage is 10 mg once daily. Depending on individual patient response, the dose may be increased to a maximum of 20 mg daily. Long term treatment of responders has been studied for at least 6 months and can be considered on an individual basis to prevent relapse.

Obsessive compulsive disorder (OCD):

Usual dosage is 10 mg once daily. Depending on individual patient response, the dose may be increased to 20 mg daily. Long term treatment of patients responding to a 16-week open treatment phase has been studied for at least 24 weeks in patients receiving 10 or 20 mg/day. As OCD is a chronic disease, patients should be treated for a sufficient period to ensure that they are symptom free. This period may be several months or even longer.

Special populations

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.

Reduced hepatic function:

Dosages should be halved to the lower end of the dose range in patients with hepatic insufficiency (see section 4.4).

Paediatric population

Children and adolescents (< 18 years of age):

ZYTOMIL should not be used in the treatment of children and adolescents under the age of 18 years (see section 4.3).

Method of administration

ZYTOMIL is administered as a single daily dose.

ZYTOMIL may be taken with or without food in the morning or evening.

Missed dose

Medical practitioners should advise patients who forget to take ZYTOMIL to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to

compensate for the missed dose.

Discontinuation symptoms when stopping treatment:

When stopping ZYTOMIL therapy, gradual dose reduction over a period of one to two weeks should be considered in order to reduce the risk of discontinuation symptoms (see section 4.4).

4.3 Contraindications

ZYTOMIL is contraindicated in:

- hypersensitivity to escitalopram or to any of the ingredients of ZYTOMIL
- children under 18 years of age (see section 4.4)
- monoamine oxidase inhibitors: cases of serious reactions have been reported in patients receiving an selective serotonin 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 section 4.5). Some cases presented with features resembling serotonin syndrome (see section 4.4)
- ZYTOMIL should not be used in combination with a MAOI. ZYTOMIL may be started 14 days after discontinuing treatment with a MAOI. At least 7 days should elapse after discontinuing ZYTOMIL treatment before starting a MAOI (see section 4.5)
- ZYTOMIL is contraindicated in patients with known QT interval prolongation or congenital long QT syndrome
- ZYTOMIL is contraindicated together with medicines that are known to prolong the QT interval (see section 4.5)
- concomitant treatment with pimozide as the combination may lead to clinically significant QTc prolongation (see section 4.5)
- concomitant treatment with linezolid (see section 4.5)
- porphyria (see section 4.4)
- pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Suicidality or clinical worsening

Patients with major depressive disorder, both adults and children, may experience worsening of their depression and / or the emergence of suicidal ideation and behaviour, whether or not they are taking antidepressant medicines. This risk may persist until significant remission occurs. A causal role, however, for antidepressant medicine in inducing such behaviour has not been established. Patients being treated with ZYTOMIL should, nevertheless, be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy or at any time of dose changes, either increases or decreases.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorders should be observed when treating patients with other psychiatric and non-psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicide attempts and should receive careful monitoring during treatment.

A meta-analysis of placebo controlled clinical trials of antidepressant medicines in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany ZYTOMIL, especially in early treatment and following dose changes.

Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

The following symptoms have been reported in patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia, hypomania, and mania.

QT interval prolongation

Escitalopram has been found to cause a dose-dependent prolongation of the QT interval. Cases of QT interval prolongation and ventricular dysrhythmia including torsade de pointes have been reported, predominantly in patients of female gender, with hypokalaemia, or with pre-existing QT interval prolongation or other cardiac diseases (see sections 4.3, 4.8 and 4.9).

Patients with significant bradycardia; or patients with recent acute myocardial infarction or uncompensated heart failure must be treated with ZYTOMIL with caution.

Hypokalaemia and hypomagnesaemia increase the risk for malignant dysrhythmias and therefore all electrolyte disturbances should be corrected before treatment with ZYTOMIL is initiated. 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 escitalopram, the treatment should be withdrawn and an ECG should be performed.

Withdrawal

Abrupt discontinuation of ZYTOMIL can lead to discontinuation effects. In general, withdrawal reactions tend to occur within 3 days of stopping treatment (see section 4.2), however, there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. The most common reported reactions are dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability and visual disturbances. These events are mild to moderate and are self-limiting (usually resolving within 2 weeks), however, in some patients they may be severe and/ or prolonged (2 - 3 months or more). It is therefore advised that when ZYTOMIL treatment is no longer required, gradual discontinuation by dose tapering should be carried out over a period of several weeks or months, according to the patient's needs (see section 4.2).

Elderly patients (> 65 years of age)

A longer half-life (about 50 %) and decreased clearance values have been demonstrated in the elderly

due to a reduced rate of metabolism. A lower initial and maximum dose should be considered.

Hepatic impairment

Clearance of ZYTOMIL is reduced. Dosages should be halved to the lower end of the dosage range in patients with hepatic insufficiency (see section 4.2). When stopping ZYTOMIL therapy, gradual dose reduction should be considered.

Seizures or history thereof

There is an increased risk of seizures. ZYTOMIL should be discontinued in any patient who develops seizures for the first time. ZYTOMIL should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. ZYTOMIL should be discontinued if there is an increase in seizure frequency.

Electroconvulsive therapy (ECT)

There is limited published clinical experience of concurrent administration of ZYTOMIL and ECT, therefore caution is advised in patients receiving electroconvulsive therapy.

Mania or history of mania

Condition may be re-activated. ZYTOMIL should be discontinued in any patient entering a manic phase. ZYTOMIL should be used with caution in patients with a history of mania/hypomania.

Cardiac Conditions

ZYTOMIL may cause a reduction in heart rate. Caution is advised in patients with pre-existing slow heart rates.

Diabetes mellitus

Occurrences of hypoglycaemia have been reported. In patients with diabetes mellitus treatment with ZYTOMIL 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.

Paradoxical anxiety

Some patients with panic disorder may experience increased anxiety symptoms at the start of treatment with ZYTOMIL. 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.

Akathisia/psychomotor restlessness

The use of SSRIs such as ZYTOMIL has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move, often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental, the use of ZYTOMIL may need to be reviewed.

Hyponatraemia

Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported and may resolve on discontinuation of therapy. Caution should be exercised in patients at risk, such as the elderly, or patients with cirrhosis, or if ZYTOMIL is used in combination with other medicines which may cause hyponatraemia.

Haemorrhage

There have been reports of cutaneous bleeding abnormalities, such as ecchymosis and purpura, with ZYTOMIL. Caution is advised in patients taking ZYTOMIL, particularly in concomitant use with medicines known to affect platelet function, e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), as well as in patients with a history of bleeding disorders (see section 4.5).

Postpartum haemorrhage

SSRIs, such as ZYTOMIL, may increase the risk of postpartum haemorrhage (see sections 4.6 and 4.8).

Risk of serotonin syndrome

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

There have been reports of enhanced effects when ZYTOMIL has been given with lithium or tryptophan and therefore concomitant use of ZYTOMIL with these medicines should be undertaken with caution (see section 4.3).

Angle-closure glaucoma

SSRIs, including ZYTOMIL, may have an effect on pupil size resulting in mydriasis. This mydriatic effect has the potential to narrow the eye angle resulting in increased intraocular pressure and angle-closure glaucoma, especially in patients pre-disposed. ZYTOMIL should therefore be used with caution in patients with angle-closure glaucoma or history of glaucoma.

Concomitant medicines

ZYTOMIL should not be used with monoamine oxidase inhibitors, imipramine, other serotonergic medicines, moclobemide, alcohol, warfarin, and cimetidine (see section 4.5).

St. John's Wort

Concomitant use of ZYTOMIL with herbal remedies containing St. John's Wort (*Hypericum perforatum*) may result in an increased incidence of adverse reactions (see section 4.5).

Bone fractures

An increased risk of bone fractures has been observed in patients aged 50 years or older taking ZYTOMIL. The mechanism leading to this risk is unknown.

Sexual dysfunction

Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRIs.

Paediatric population

Safety and efficacy in children under 18 years of age have not been established. In clinical trials in major depressive disorder, there were increased reports of hostility and suicide-related adverse events such as suicidal ideation and self-harm (see section 4.3).

Information on excipients of ZYTOMIL

ZYTOMIL contains sodium.

This medicine contains less than 1 mmol (0,023 g) sodium per tablet, that is to say essentially 'sodium free'.

4.5 Interaction with other medicines and other forms of interaction

Escitalopram, as in ZYTOMIL, 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, as in ZYTOMIL, is a weak inhibitor of isoenzyme CYP1A2, 2C9, 2C19, 2E1, and 3A, and weak inhibitor of 2D6.

- **Ritonavir:**

  The pharmacokinetics of single doses of ZYTOMIL are 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 ZYTOMIL.

Combinations contraindicated:

- **Monoamine oxidase inhibitors (MAOIs):**

  Concurrent use is contraindicated. Serious and potentially fatal reactions have occurred such as: hyperthermia, rigidity, myoclonus, autonomic instability with rapid fluctuation of vital signs and mental status changes including extreme agitation progressing to delirium and coma (see section 4.3). 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 SSRI treatment and have been started on such MAOI treatment (see section 4.3). In some cases, the patient developed serotonin syndrome (see section 4.8).
  ZYTOMIL is contraindicated in combination with MAOIs. ZYTOMIL may be started 14 days after discontinuing treatment with a MAOI. At least 7 days should elapse after discontinuing ZYTOMIL treatment, before starting a MAOI.

- **Moclobemide:**

  Due to the risk of serotonin syndrome, the combination of ZYTOMIL with a MAO-A inhibitor such as moclobemide is contraindicated (see section 4.3). If the combination proves necessary, it should be started at the minimum recommended dosage and clinical monitoring should be reinforced.

- **Linezolid:**

  The antibiotic linezolid is a MAO inhibitor and is contraindicated in patients treated with ZYTOMIL (see section 4.3).

- **MAO-B inhibitor (Selegiline):**

  Racemic citalopram increased the AUC of selegiline by 29 %. The combination with selegiline is contraindicated due to the risk of developing serotonin syndrome (see section 4.3).

- **Medicines that prolong the QT interval:**

  Pharmacokinetic and pharmacodynamic studies of escitalopram combined with other medicines that prolong the QT interval have not been performed. An additive effect of escitalopram and these medicines cannot be excluded. Therefore, co-administration of escitalopram with medicines that prolong the QT interval, such as Class IA and III antidysrhythmics, antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, antimalarial treatment particularly halofantrine), certain antihistamines (e.g. astemizole, mizolastine) is contraindicated (see section 4.3).
  Cases of QT interval prolongation and ventricular arrhythmia 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 disease (see sections 4.3, 4.4, 4.8 and 4.9).

- **Pimozide:**

  Co-administration of a single dose of pimozide 2 mg to subjects treated with racemic citalopram 40 mg/day for 11 days caused an increase in AUC and C_{max} of pimozide. The co-administration of pimozide and citalopram results in a mean increase in the QTc interval of approximately 10 msec. Due to the interaction noted at a low dose of pimozide, concomitant administration of citalopram and pimozide is contraindicated.

Combinations requiring precautions for use:

- **Cimetidine:**

  Co-administration of racemic citalopram with cimetidine (potent CYP2D6, 3A4 and 1A2 inhibitor) results 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 ZYTOMIL when used concomitantly with high doses of cimetidine.

- **Monoamine oxidase inhibitors (MAOIs), Sumatriptan and Tramadol:**

  Co-administration with a MAOI may cause serotonin syndrome. Co-administration with other

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

There have been reports of enhanced effects when ZYTOMIL has been given with lithium or tryptophan and therefore concomitant use of ZYTOMIL with these medicines should be undertaken with caution (see section 4.4).

- **Medicines lowering the seizure threshold:**

  SSRIs, such as ZYTOMIL, can lower the seizure threshold. Caution is advised when concomitantly using other medicines capable of lowering the seizure threshold (e.g. other antidepressants (tricyclics, SSRIs), neuroleptics (phenothiazines, thioxanthenes and butyrophenones), mefloquine, bupropion and tramadol).

- **Desipramine:**

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

- **Metoprolol:**

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

- **St John's Wort:**

  Concomitant use of SSRIs, such as ZYTOMIL, and herbal remedies containing St. John's Wort (*Hypericum perforatum*) may result in an increased incidence of adverse reactions (see section 4.4).

- **Alcohol:**

  Alcohol may increase the central nervous system (CNS) side effects of ZYTOMIL. The combination with alcohol is not advisable (see section 4.8).

- **Medicines inducing hypokalaemia / hypomagnesaemia:**

  Caution is warranted for concomitant use of hypokalaemia / hypomagnesaemia inducing medicines, as these conditions increase the risk of malignant dysrhythmias (see section 4.4).

- **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) and digoxin. However, prothrombin time was slightly increased after a single dose of warfarin 25 mg. The international normalised ratio (INR) needs to be carefully monitored in patients on the combination. Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and other medicines affecting coagulation may increase bleeding tendency (see section 4.4).

  Caution is to be exercised during concomitant use of the following: Flecainide, propafenone, clomipramine, nortriptyline, risperidone, thioridazine and haloperidol due to lowering of the seizure threshold.

4.6 Fertility, pregnancy and lactation

Pregnancy

ZYTOMIL is contraindicated in pregnancy (see section 4.3). Safety and efficacy in pregnancy have not been established.

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see sections 4.4 and 4.8).

Using ZYTOMIL in the third trimester may result in effects, including neurobehavioral disturbances, in the newborn infant. The following symptoms may occur in the newborn after maternal SSRI/SNRI use, such as ZYTOMIL, in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These symptoms could be due to either discontinuation effects or excess serotonergic

activity. In a majority of instances, such complications begin immediately or soon (< 24 hours) after delivery. Epidemiological data have suggested that the use of SSRIs such as ZYTOMIL in pregnancy, particularly in late pregnancy may increase the risk of persistent pulmonary hypertension in the newborn (PPHN).

Breastfeeding

ZYTOMIL is contraindicated during lactation (see section 4.3). Safety and efficacy during lactation have not been established. ZYTOMIL is excreted into the breast milk. Consequently, breastfeeding is not recommended during treatment.

Neonates should be observed if maternal use of ZYTOMIL continues into the later stages of pregnancy, particularly in the third trimester.

Fertility

Animal data have shown that some SSRIs may affect sperm quality. Human case reports with some SSRIs have shown that an effect on sperm quality is reversible. Impact on human fertility has not been observed so far.

4.7 Effects on ability to drive and use machines:

ZYTOMIL may impair performance of skilled tasks. Patients who are depressed and require treatment may have an impaired ability to drive or operate machinery. Patients should be warned of this possibility and advised to avoid such tasks if so affected (see section 4.8).

4.8 Undesirable effects

a). Summary of the safety profile

Adverse reactions observed with ZYTOMIL 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 ZYTOMIL may produce withdrawal reactions in some patients.

b). Tabulated list of adverse reactions

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	*Frequency unknown*	Thrombocytopaenia
Immune system disorders	*Less frequent*	Angioedema, anaphylactoid reactions
Endocrine disorders	*Frequency unknown*	Inappropriate antidiuretic hormone (ADH) secretion
Metabolism and nutrition disorders	*Frequent* *Less Frequent* *Frequency unknown*	Decrease appetite, increased appetite, weight increased Weight decreased Hyponatraemia, aneroxia
Psychiatric disorders	*Frequent* *Less frequent* *Frequency unknown*	Anxiety, restlessness, abnormal dreams, libido decreased Bruxism, agitation, nervousness, panic attack, confusional state, aggression, depersonalisation, hallucination Mania, hostility, suicidal ideation and self-harm have been reported in children

Nervous system disorders	*Frequent*	Sleep disturbances, somnolence, dizziness, insomnia, drowsiness, paraesthesia, tremor
	Less frequent	Taste disturbances, sleep disorder, syncope, 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 inco-ordination)
	Frequency unknown	Headache, impaired concentration, malaise, dyskinesia, seizures, movement disorders, psychomotor restlessness/akathisia
Eye disorders	*Less frequent*	Mydriasis
	Frequency unknown	Accommodation disturbances, abnormal vision
Ear and labyrinth disorders	*Less frequent*	Tinnitus

Cardiac disorders	*Less frequent* *Frequency unknown*	Tachycardia, bradycardia Palpitations, tremor, electrocardiogram QT prolonged ventricular dysrhythmia including *torsade de pointes*
Vascular disorders	*Frequency unknown*	Postural hypotension
Respiratory, thoracic and mediastinal disorders	*Frequent* *Less frequent*	Sinusitis, yawning Nasal congestion, rhinitis, influenza-like symptoms, epistaxis
Gastrointestinal disorders	*Frequent* *Less frequent* *Frequency unknown*	Nausea, constipation, diarrhoea, dry mouth, vomiting, indigestion Abdominal pain, gastrointestinal haemorrhages (including rectal haemorrhage) Salivation
Hepatobiliary disorders	*Frequency unknown*	Hepatitis, abnormal liver function tests

Skin and subcutaneous tissue disorders	*Frequent*	Increased sweating
	Less frequent	Urticaria, alopecia, rash, pruritus
	Frequency unknown	Ecchymosis, angioedema's
Musculoskeletal, connective tissue and bone disorders	*Frequent*	Arthralgia, myalgia
	Frequency unknown	Asthenia
Renal and urinary disorders	*Frequency unknown*	Urinary retention
Reproductive system and breast disorders	*Frequent*	Sexual dysfunction including ejaculation disorder and impotence (male), abnormal orgasm (female), decreased libido
	Less frequent	Anorgasmia, metrorrhagia, menorrhagia
	Frequency unknown	Galactorrhoea, priapism, postpartum haemorrhage[2]
General disorders and administrative site conditions	*Frequent*	Fatigue, pyrexia
	Less frequent	Oedema

c. Description of selected adverse reaction

[1] Cases of suicidal ideation and suicidal behaviours have been reported during escitalopram therapy

or early after treatment discontinuation (see section 4.4).

[2] This event has been reported for the therapeutic class of SSRIs/SNRIs (see sections 4.4 and 4.6).

Cases of QT-prolongation have been reported during the post-marketing period, predominantly in patients with pre-existing cardiac disease. 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 ZYTOMIL may produce withdrawal reactions in some patients.

Discontinuation symptoms seen when stopping treatment

Discontinuation of SSRIs/SNRIs (particularly when abrupt) commonly leads to discontinuation symptoms. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances are the most commonly reported reactions. Generally, these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when ZYTOMIL treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2 and 4.4).

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. Healthcare professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website. An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 OVERDOSE

Signs and symptoms:

Symptoms are mainly related to the central nervous system (ranging from dizziness, tremor and agitation to rare cases of serotonin syndrome, convulsion and coma), the gastrointestinal system (nausea/vomiting), and the cardiovascular system (hypotension, tachycardia, QT interval prolongation and dysrhythmia) and electrolyte/fluid balance conditions (hypokalaemia, hyponatraemia).

Management of overdose:

There is no specific antidote. Treatment is supportive and symptomatic. The stomach should be emptied as soon as possible by emesis. Establish and maintain an airway, ensure adequate oxygenation and respiratory function. Gastric lavage and the use of activated charcoal should be carried out as soon as possible after oral ingestion. Monitoring of cardiac and vital signs are necessary and medical surveillance is advisable for about 24 hours, along with general symptomatic supportive measures. Electrocardiogram (ECG) monitoring is advised in case of overdose in patients with congestive heart failure / brady-dysrhythmias, in patients using concomitant medicines that prolong the QT interval, or in patients with altered metabolism, e.g. liver impairment (see section 4.8).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressants, selective serotonin reuptake inhibitors

ATC code: N06AB10

Pharmacological classification: A 1.2 Psychoanaleptics (antidepressants)

Mechanism of action

Escitalopram is the (S)-enantiomer of citalopram, a bicyclic phthalane derivative with antidepressant effect. Escitalopram is a selective inhibitor of serotonin (5-HT) reuptake.

Escitalopram blocks 5-HT reuptake, leading to potentiation of serotonergic activity in the central nervous system (CNS).

Escitalopram has minimal effect on Escitalopram has minimal effect on norepinephrine noradrenaline (NA) (norepinephrine), dopamine (DA) and gamma aminobutyric acid (GABA) reuptake. Escitalopram also has little or no antidopaminergic, antiadrenergic, antiserotonergic, antihistaminergic or anticholinergic properties.

Escitalopram has no or very low affinity for a series of receptors including 5-HT1A, 5-HT2, DA, D1 and D2 receptors, α1, α2-, β- adrenoceptors, histamine H1, muscarinic receptors, benzodiazepine and opioid receptors.

5.2 Pharmacokinetic properties

Absorption:

The mean T_{max} is 4 hours after oral absorption. Absorption is independent of food intake. The area under the plasma or serum concentration time curve from time zero to 24 hours and C_{max} is both linear and proportional to the dose of escitalopram.

Distribution:

The volume of distribution of escitalopram is about 12 –- 26 L/kg and binds approximately 55 % to plasma proteins.

Biotransformation:

Demethylated and didemethylated metabolites of escitalopram are produced in the liver as well as an 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 demethylated and the didemethylated 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 primary route of elimination of escitalopram is as metabolites via the urine. The elimination

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

Linearity/non-linearity:

Escitalopram exhibits linear pharmacokinetics. Steady state plasma levels are achieved in about 1 week. With a daily dose of 10 mg, average steady state concentrations of 50 nmol/L (range 20 - 125 nmol/L) are achieved.

Pharmacokinetics in special patient groups

Elderly patients (> 65 years of age):

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

Reduced hepatic function:

Elimination of escitalopram occurs more slowly in patients with reduced liver function. In the case of hepatic impairment, the half-life of escitalopram is twice as long, 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 in renal function. There is no major impact on escitalopram concentrations in serum. There is no information on the treatment of patients with severe renal impairment (creatinine clearance of < 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.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide

Croscarmellose sodium

Hydroxypropyl methylcellulose

Magnesium stearate

Microcrystalline cellulose

Coating:

Hydroxypropyl methylcellulose

Polyethylene glycol

Talc

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 30°C. Protect from light.

Keep blisters in outer carton until required for use.

Keep bottles tightly closed.

6.5 Nature and contents of container

ZYTOMIL is packed into hard, silver-coloured aluminium foil/clear transparent PVC/PVDC or PVC/PE/PVDC film blister strips inside an outer carton containing 30 tablets.

ZYTOMIL is also packed into white, HDPE bottles with a desiccant, polyester pharmcoil and a white PP screw cap with 30 tablets inside.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

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8. REGISTRATION NUMBERS

ZYTOMIL 10 mg: A42/1.2/0912

ZYTOMIL 20 mg: A42/1.2/0914

9. DATE OF RENEWAL OF THE AUTHORISATION

30 April 2010

10. DATE OF REVISION OF THE TEXT

20 November 2023

NAMIBIA:

ZYTOMIL 10 mg: NS3 10/1.2/0479

ZYTOMIL 20 mg: NS3 10/1.2/0481

MOZAMBIQUE:

ZYTOMIL 10: N5935

ZYTOMIL 20: N5936