SCHEDULING STATUS S5

1 NAME OF THE MEDICINE

ADCO TALOMIL 10 mg, 10 mg film-coated tablets
ADCO TALOMIL 20 mg, 20 mg film-coated tablets
ADCO TALOMIL 40 mg, 40 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ADCO TALOMIL 10 mg: Each film-coated tablet contains citalopram hydrobromide equivalent to 10 mg citalopram.
ADCO TALOMIL 20 mg: Each film-coated tablet contains citalopram hydrobromide equivalent to 20 mg citalopram.
ADCO TALOMIL 40 mg: Each film-coated tablet contains citalopram hydrobromide equivalent to 40 mg citalopram.

ADCO TALOMIL 10 mg: Contains sugar (mannitol): 66,275 mg
ADCO TALOMIL 20 mg: Contains sugar (mannitol): 132,55 mg
ADCO TALOMIL 40 mg: Contains sugar (mannitol): 265,10 mg

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.
ADCO TALOMIL 10 mg: Round, biconvex, unscored, 6 mm, coated, white tablets.
ADCO TALOMIL 20 mg: Round, biconvex, scored on both sides with side scores, 8 mm, coated, white tablets.
ADCO TALOMIL 40 mg: Round, biconvex, scored on both sides with side scores, 10 mm, coated, white tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ADCO TALOMIL is indicated for the treatment of:

- Depression and prevention of relapse.
- Panic disorder, with or without agoraphobia.
- Obsessive-compulsive disorder (OCD).

4.2 Posology and method of administration

Posology

Adults

Treating depression

A single oral dose of 20 mg **ADCO TALOMIL** should be administered daily. This dose may be increased to a maximum of 40 mg daily, as determined by the response of the individual patient.

Duration of treatment: The antidepressant effect usually sets in after 2 to 4 weeks. Treatment with **ADCO TALOMIL** is symptomatic and must therefore be continued for an appropriate length of time, usually up to 6 months after recovery in order to prevent relapse.

Treating panic disorder
For the first week a single dose of 10 mg is recommended, before increasing the dose to 20 mg daily. Depending on individual patient response, this dose may be further increased to a maximum of 40 mg daily.

Treating obsessive-compulsive disorder (OCD)
An initial dose of 20 mg daily as a single dose is recommended. This dose can be increased to a maximum of 40 mg daily, depending on the patient's response.
Duration of treatment: The onset of action in treating OCD is 2 to 4 weeks with further improvement over time.

Withdrawal symptoms seen on discontinuation
Abrupt discontinuation should be avoided. The dose of **ADCO TALOMIL** should be gradually reduced over a period of at least one or two weeks in order to reduce the risk of withdrawal symptoms (see section 4.4 and 4.8).

If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the medical practitioner may continue decreasing the dose, but at a more gradual rate.

Special populations
Elderly patients (> 65 years)
For elderly patients, the dose should be decreased to half of the recommended dose: 10 to 20 mg daily as a single dose. The recommended maximum daily dose for elderly patients is 20 mg.

Children and adolescents (18 years)
The use of **ADCO TALOMIL** is not recommended as safety and efficacy have not been established in this age group.

Dosage in renal impairment
No dosage adjustment is required in cases of mild or moderate renal impairment. **ADCO TALOMIL** is contraindicated in patients with severe renal impairment (creatinine clearance less than 30 mL/min) (see section 4.3 and 5.2).

Dosage in hepatic impairment
An initial dose of 10 mg daily for the first two weeks of treatment is recommended in patients with mild or moderate hepatic impairment. Depending on individual patient response, the dose may be increased to a maximum of 20 mg daily. Caution and extra careful dose titration is advised in patients with severely reduced hepatic function.

Poor metabolisers of CYP2C19
An initial dose of 10 mg daily during the first two weeks of treatment is recommended for patients who are known to be poor metabolisers with respect to CYP2C19. The dose may be increased to a maximum of 20 mg daily, depending on individual patient response.

Method of administration
ADCO TALOMIL tablets can be taken in the morning or evening, not necessarily with food.
ADCO TALOMIL tablets are administered as a single daily dose.

4.3 Contraindications
- Hypersensitivity to citalopram or to any of the excipients of **ADCO TALOMIL** (see section 6.1).
- Children under 18 years of age (see section 4.4).
- Severely impaired renal function (creatinine clearance < 30 mL/min).
- Pregnancy and lactation, as safety has not yet been established.
- Concurrent use with a monoamine oxidase inhibitor (MAOI). At least 14 days should elapse between discontinuing the monoamine oxidase inhibitor (MAOI) and initiating therapy with **ADCO TALOMIL**. Monoamine oxidase inhibitors (MAOI's) should not be introduced for 7 days after discontinuation of **ADCO TALOMIL** (see section 4.5).
- Concurrent use with linezolid (see section 4.5).
- Concurrent use with pimozide (see section 4.5).
- Patients with known QT interval prolongation or congenital long QT syndrome (see section 4.4 and 4.8).
- Concurrent use with other medicines that are known to prolong the QT interval (see section 4.5).

4.4 Special warnings and precautions for use
Suicide/suicidal thoughts 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 still persist until significant remission occurs. A causal role, however, for antidepressant medicines in inducing such behaviour has not been established. Patients being treated with **ADCO TALOMIL** 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 disorder should be observed when treating patients with other psychiatric and non-psychiatric disorders.
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). Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing **ADCO TALOMIL**, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision is made to discontinue treatment, **ADCO TALOMIL** should be tapered (see section 4.2 and 4.8).
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.

Use in children and adolescents under 18 years of age
Safety and efficacy in children and adolescents under 18 years of age have not been established. Suicide related behaviours (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed among children and adolescents treated with antidepressants compared to those treated with placebo (see section 4.3 and 4.8). In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Monoamine oxidase inhibitors (MAOIs)
Patients receiving monoamine oxidase inhibitors (MAOIs) should not be treated concomitantly with **ADCO TALOMIL** and for 14 days after treatment with MAOIs has been discontinued. Treatment with MAOIs should be delayed for 7 days after **ADCO TALOMIL** has been discontinued (see section 4.5).

Elderly patients
Longer half-life and decreased clearance due to a reduced rate of metabolism have been demonstrated in elderly patients. A lower dose is recommended in the elderly (see section 4.2).

Hepatic impairment
Clearance of **ADCO TALOMIL** is reduced in patients with hepatic impairment. Cautious dosage titration and a lower maximum dose are recommended (see section 4.2).

Renal impairment
Elimination is decreased in patients with renal impairment. If creatine clearance is less than 30 mL/min **ADCO TALOMIL** should not be used (see section 4.3).

Paradoxical anxiety
Some patients with panic disorder may experience intensified anxiety symptoms at the start of treatment with antidepressants. This paradoxical reaction usually subsides within the first

two weeks of starting treatment. A low starting dose of **ADCO TALOMIL** is advised to reduce the likelihood of a paradoxical anxiogenic effect.

Hyponatraemia
Hyponatraemia, probably due to syndrome of inappropriate antidiuretic hormone secretion (SIADH), has been reported as a rare adverse reaction with the use of SSRIs and generally reverses on discontinuation of therapy. Elderly female patients seem to be at higher risk.

Akathisia/psychomotor restlessness
The use of SSRIs/SNRIs 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 of **ADCO TALOMIL** may be detrimental.

Seizures
Seizures are a potential risk with antidepressant medicines. **ADCO TALOMIL** should be discontinued in any patient who develops seizures. **ADCO TALOMIL** should be used with caution in patients with controlled epilepsy and avoided in patients who are poorly-controlled epileptics. Care is advised in patients receiving electroconvulsive therapy or where there is an increase in seizure frequency.

Mania
In patients with mania or a history of mania, a change towards the manic phase may occur. **ADCO TALOMIL** should be discontinued if the patient enters the manic phase.

Heart conditions
ADCO TALOMIL may cause a reduction in heart rate. Caution is advised in patients with pre-existing slow heart rates.

Diabetes mellitus
In patients with diabetes, treatment with **ADCO TALOMIL** may alter glycaemic control. Dosage of insulin and/or oral hypoglycaemic medicine may need to be adjusted.

Serotonin syndrome
Serotonin syndrome has been reported in patients using SSRIs. A combination of symptoms such as agitation, tremor, myoclonus and hyperthermia may indicate the development of this condition. Treatment with **ADCO TALOMIL** should be discontinued immediately and symptomatic treatment initiated.

Serotonergic medicines
ADCO TALOMIL should not be used concomitantly with medicines with serotonergic effects such as sumatriptan or other triptans, tramadol, oxitriptan and tryptophan (see section 4.5).

Haemorrhage
There have been reports of prolonged bleeding time and/or bleeding abnormalities such as ecchymoses, gynaecological haemorrhages, gastrointestinal bleeding and other cutaneous or mucous bleedings with SSRIs (see section 4.8). SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see section 4.6 and 4.8). Caution is advised in patients taking **ADCO TALOMIL**, particularly with concomitant use of medicines known to affect platelet function or other active substances that can increase the risk of haemorrhage, as well as in patients with a history of bleeding disorders (see section 4.5).

St John's wort
Undesirable effects may be more common during concomitant use of **ADCO TALOMIL** and herbal preparations containing St John's wort (*Hypericum perforatum*). Therefore, **ADCO TALOMIL** and St John's wort preparations should not be taken concomitantly (see section 4.5).

Psychosis
Treatment of psychotic patients with depressive episodes may increase psychotic symptoms.

QT interval prolongation
ADCO TALOMIL 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 during the post-marketing period, predominantly in female patients, with hypokalaemia, or with pre-existing QT prolongation or other cardiac diseases (see section 4.3, 4.5 and 4.8).
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 for malignant dysrhythmias and should be corrected before treatment with **ADCO TALOMIL** is started.
If patients with stable cardiac disease are treated, an electrocardiogram (ECG) review should be considered before treatment is started. ECG monitoring may be advisable in case of overdose or conditions of altered metabolism with increased peak levels, e.g. liver impairment.
If signs of cardiac dysrhythmia occur during treatment with **ADCO TALOMIL**, the treatment should be withdrawn and an ECG should be performed.

Withdrawal symptoms
After prolonged administration, abrupt cessation of **ADCO TALOMIL** may produce withdrawal symptoms such as dizziness, sensory disturbances (including paraesthesia), 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 symptoms are not indicative of addiction.

It is recommended that withdrawal of treatment should proceed by gradually tapering off the dosage over a period of several weeks or months, according to the patient's needs to avoid occurrence of discontinuation symptoms.

4.5 Interaction with other medicines and other forms of interaction

- Concomitant use of monoamine oxidase inhibitors (MAOIs), including selegiline, linezolid and moclobemide - 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).
- No interaction with lithium was reported.
- Citalopram interacts with imipramine - an increase in the concentration of desimipramine (the active metabolite of imipramine) may occur. It appears that **ADCO TALOMIL** does not cause a marked increase in plasma levels of some tricyclic antidepressants. Concomitant administration with other antidepressants may result in severe adverse reactions including the serotonin syndrome, a rare but potentially fatal hyperserotonergic state. At least one week should elapse between discontinuing a selective serotonin reuptake inhibitor (SSRI) and starting any medicine liable to provoke a serious reaction (e.g. phenelzine).
- Moclobemide – serotonin syndrome has developed after taking overdoses of moclobemide and **ADCO TALOMIL**.
- Citalopram interacts with selegiline and sumatriptan.
- Citalopram has a weak inhibitory effect on sparteine metabolism which decreases the elimination of agents which are dependent on sparteine oxygenase to a minor degree.
- The combination of **ADCO TALOMIL** and alcohol is not recommended. The effects of alcohol may be increased.
- Warfarin – the anticoagulant activity of warfarin may be increased.
- Cimetidine – the AUC and the maximum plasma concentration of **ADCO TALOMIL** are increased when **ADCO TALOMIL** is administered concurrently with cimetidine.
- In clinical studies where citalopram was given concomitantly with benzodiazepines, neuroleptics, analgesics, antihistamines, antihypertensive agents, betablockers and other cardiovascular agents, no pharmacodynamic interactions were reported.
- In view of the fact that about 80 % of citalopram in plasma is protein bound, the potential for interactions with agents that are highly protein bound is thought to be minimal.
- Co-administration with serotonergic medicines (e.g. tramadol, sumatriptan) may lead to enhancement of 5-HT associated effects. The simultaneous use of **ADCO TALOMIL** and 5-HT agonists, such as sumatriptan and other triptans, is not recommended (see section 4.4).
- St John's wort – pharmacodynamic interactions between SSRIs such as **ADCO TALOMIL** and the herbal remedy St John's wort (*Hypericum perforatum*) can occur, resulting in an increase in undesirable effects (see section 4.4). Pharmacokinetic investigations have not been investigated.
- Haemorrhage – simultaneous treatment with anticoagulants, medicines that affect the platelet function, such as non-steroidal anti-inflammatory medicines (NSAIDs),

acetylsalicylic acid, dipyridamole and ticlopidine or other medicines (e.g. atypical antipshychotics, phenothiazines, tricyclic antidepressants) can increase the risk of haemorrhage (see section 4.4).

- An additive effect of citalopram, as in **ADCO TALOMIL**, and medicines that prolong the QT interval cannot be excluded. Therefore, co-administration of **ADCO TALOMIL** with these medicines, 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, anti-malarial treatment particularly halofantrine), certain antihistamines (astemizole, mizolastine) etc. is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

The safety and efficacy of **ADCO TALOMIL** in pregnancy and lactation have not been established. **ADCO TALOMIL** is excreted into breast milk.

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

4.7 Effects on ability to drive and use machines

ADCO TALOMIL does not have negative effects on intellectual function or psychomotor performance. Nevertheless, patients who are depressed and receive **ADCO TALOMIL** treatment may have impaired ability to drive or operate machinery. Patients should be warned of this possibility and advised not to drive or operate machinery if they are affected.

4.8 Undesirable effects

The following adverse events were more commonly observed in patients receiving citalopram, than in patients treated with placebo: sweating, somnolence, nausea, tremor, dry mouth and asthenia.

The intensity and frequency of adverse events usually decrease with improvement of the depressive state. Clinical evidence shows that tachycardia or postural hypotension is not associated with citalopram. A decrease in pulse rate has been observed. In children, there have been reports of hostility, suicidal ideation and self-harm. The abrupt discontinuation of citalopram may precipitate adverse effects such as anxiety, headache, migraine, paraesthesia and tremor (see section 4.2).

System organ class	**Frequent**	**Less frequent**	**Frequency unknown**
Immune system disorders			Anaphylactoid reactions
Endocrine disorders		Galactorrhoea	Hyperprolactinaemia
Metabolism and nutrition disorders		Hyponatraemia (particularly in the elderly), anorexia, weight changes	

Psychiatric disorders		Anxiety, panic attacks, hypomania, mania	Hostility, aggressiveness, impulsivity, akathisia and suicidal ideation
Nervous system disorders	Sleep disturbances (insomnia, drowsiness), restlessness, nervousness, somnolence, sexual dysfunction (decreased libido, ejaculation disorder), anorgasmia	Agitation, confusion, impaired concentration, convulsions, extrapyramidal effects, tremor	Paraesthesia, headache, dizziness, irritability, serotonin syndrome, neuroleptic malignant syndrome
Eye disorders		Mydriasis, accommodation disturbances	
Cardiac disorders	Palpitations	Bradycardia, tachycardia	QT prolongation, ventricular dysrhythmia (including torsade de pointes)
Vascular disorders		Ecchymosis, purpura, orthostatic hypotension	
Respiratory, thoracic and mediastinal disorders		Nasal congestion, yawning	
Gastro-intestinal disorders	Nausea, dry mouth	Hypersalivation, vomiting, diarrhoea, dyspepsia	Constipation
Hepato-biliary disorders			Hepatitis, hepatic necrosis, abnormal liver function tests
Skin and subcutaneous tissue disorders		Rash, pruritus, sweating	Photosensitivity, urticaria, angioedema, alopecia
Musculo-skeletal and connective tissue disorders		Arthralgia, myalgia, asthenia	
Renal and urinary disorders		Micturition	Urinary retention

Reproductive system and breast disorders			Postpartum haemorrhage*
General disorders and administrative site conditions		Fatigue	Malaise

*This event has been reported for the therapeutic class of SSRIs/SNRIs (see section 4.4 and 4.6).

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 Reporting Form**" found online under SAHPRA's publications: http://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

(See section 4.4 and 4.8).

Should overdosage occur, it may give rise to tiredness, weakness, sedation, dizziness, tremor, nausea, somnolence and sinus tachycardia. Gastric lavage should be performed as soon as possible after oral ingestion. Monitoring of cardiac and vital signs is necessary and medical surveillance is advisable for a period of 24 hours. Treatment is symptomatic and supportive. There is no specific antidote to **ADCO TALOMIL**.

5 PHARMACOLOGICAL PROPERTIES ~~ACTION~~

5.1 Pharmacodynamic properties

A 1.2 Psychoanaleptics (antidepressants)

Pharmacotherapeutic group: Antidepressants, selective serotonin reuptake inhibitors, ATC code: N06AB04.

Citalopram is a bicyclic phthalane derivative which has antidepressant effects. As a racemic compound, one of the enantiomers is responsible for the pharmacodynamic effect which is specifically related to a selective inhibition of serotonin (5-HT)-uptake. The uptake of noradrenaline, dopamine or gamma aminobutyric acid are not affected by citalopram, and neither citalopram nor its metabolites have antidopaminergic, antiadrenergic, antiserotoninergic, antihistaminergic or anticholinergic (antimuscarinic) properties. The (5-HT)-uptake inhibitory efficacy remains unchanged after prolonged treatment and at the recommended dosages no changes in the density of neurotransmitter receptors are induced. Citalopram also does not influence the cardiac conduction system, blood pressure or complete blood count.

5.2 Pharmacokinetic properties

Pharmacokinetic data are based on findings obtained with the racemic compound. Oral bioavailability is high (> 80 %), and maximum plasma levels are reached within 4 hours (range 1 to 6 hours) of administration. A linear relationship is known to exist between steady-state

plasma levels and administered dose, which can vary by a factor of four between individuals receiving the same dose. Steady-state levels are attained within a period of 1 to 2 weeks. Citalopram has a volume of distribution of about 14 L/kg. About 80 % of the compound is protein bound.
In plasma, unchanged citalopram is the predominant compound. While its metabolites have the same pharmacological effect as citalopram, they are less potent. It is uncertain if the kinetics of the active enantiomer differ in patients who metabolise sparteine/debrisoquine or mephenytoin slowly. Citalopram has a biological half-life of approximately 36 hours (range 28 to 42 hours). Systemic plasma clearance is approximately 0,4 L/min.
Reduced metabolic rates in elderly patients may be responsible for the longer half-lives and decreased clearance values that have been observed in this group of patients, thus necessitating the use of lower doses. In patients with reduced liver function, elimination is slower. Elimination is also reduced in patients with impaired kidney function associated with low creatinine clearance. Citalopram undergoes hepatic metabolism primarily involving the cytochrome P450 3A4 (CYP3A4) and 2C19 (CYP2C19) isoenzymes and to a small extent cytochrome P450 2D6 (CYP2D6) isoenzymes. The metabolites inhibit the reuptake of serotonin, but are less potent than the parent molecule. Citalopram is excreted mainly via the liver with the remainder via the kidneys (approximately 20 % of which 12 % is unchanged medicine).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Colloidal silica anhydrous
Magnesium stearate
Mannitol
Microcrystalline cellulose
Coating:
Hypromellose
Macrogol 6000
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

ADCO TALOMIL 10 mg: 24 months
ADCO TALOMIL 20 mg: 48 months
ADCO TALOMIL 40 mg: 24 months
Store at or below 25 °C in a dry place. Keep blisters in outer carton until required for use.

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container
Blister packs of colourless, transparent plastic blisters and aluminium foil, containing 28 or 30 tablets.

6.6 Special precautions for disposal
No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION
Adcock Ingram Limited
1 New Road
Erand Gardens
Midrand, 1685
Private Bag X69
Bryanston 2021

8 REGISTRATION NUMBERS
ADCO TALOMIL 10 mg: 35/1.2/0271
ADCO TALOMIL 20 mg: 35/1.2/0272
ADCO TALOMIL 40 mg: 35/1.2/0273

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24 October 2003

10 DATE OF REVISION OF THE TEXT
19 April 2021

Namibia: ADCO TALOMIL 20 mg: NS3 04/1.2/1121